

PROSPECTUS SUPPLEMENT
(To Prospectus dated December 20, 2024)

46,868,687 Shares of Common Stock Pre-Funded Warrants to Purchase up to 25,858,586 Shares of Common Stock

We are offering 46,868,687 shares of our common stock, par value \$0.00001 per share, or the common stock and, in lieu of common stock to certain investors that so choose, pre-funded warrants to purchase up to 25,858,586 shares of our common stock. The purchase price of each pre-funded warrant will equal the price per share at which shares of our common stock are being sold to the public in this offering, minus \$0.001, the exercise price of each pre-funded warrant. Each pre-funded warrant will be immediately exercisable for one share of common stock, subject to the limitations described in the section "Description of the Pre-Funded Warrants—Exercisability." The public offering price for each share of common stock is \$2.75. We are also offering the shares of our common stock that are issuable from time to time upon exercise of the pre-funded warrants.

Our common stock is listed on The Nasdaq Global Select Market under the symbol "TSHA." The last reported sale price of our common stock on The Nasdaq Global Select Market on May 27, 2025 was \$2.605 per share. There is no established public trading market for the pre-funded warrants, and we do not expect a market to develop. We do not intend to apply for listing of the pre-funded warrants on The Nasdaq Global Select Market or any securities exchange or nationally recognized trading system. Without an active trading market, the liquidity of the pre-funded warrants will be limited.

We are an "emerging growth company" and a "smaller reporting company" under applicable Securities and Exchange Commission rules and are subject to reduced public company reporting requirements.

See "Prospectus Supplement Summary—Implications of Being an Emerging Growth Company and a Smaller Reporting Company."

Investing in our common stock involves a high degree of risk. See "[Risk Factors](#)" beginning on page S-14 of this prospectus supplement, page 6 of the accompanying prospectus and under similar headings in the documents incorporated by reference into this prospectus supplement and the accompanying prospectus.

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

	Per Share	Per Pre-Funded Warrant	Total
Public offering price	\$ 2.75	\$ 2.749	\$199,974,142
Underwriting discounts and commissions ⁽¹⁾	\$0.165	\$ 0.165	\$ 12,000,000
Proceeds to Taysha Gene Therapies, Inc., before expenses	\$2.585	\$ 2.584	\$187,974,142

(1) See "Underwriting" for a description of the compensation payable to the underwriters.

We intend to grant the underwriters an option for a period of 30 days to purchase up to 10,909,090 additional shares of our common stock at the initial price to the public less the underwriting discount.

The underwriters expect to deliver the shares and pre-funded warrants against payment in New York, New York on May 30, 2025.

Jefferies**BofA Securities****Piper Sandler****Barclays**

Prospectus Supplement dated May 28, 2025

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement is part of a “shelf” registration statement on Form S-3 (File No. 333-283801) that we filed with the Securities and Exchange Commission, or the SEC, on December 13, 2024, which was declared effective on December 20, 2024. This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this offering of common stock and pre-funded warrants and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. The information included or incorporated by reference in this prospectus supplement also adds to, updates and changes information contained or incorporated by reference in the accompanying prospectus.

Before buying any of the shares of common stock offered hereby, we urge you to read carefully this prospectus supplement and the accompanying prospectus, together with the information incorporated herein by reference as described below under the heading “Incorporation of Certain Information by Reference.” These documents contain important information that you should consider when making your investment decision. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date – for example, a document incorporated by reference in the accompanying prospectus – the statement in the document having the later date modifies or supersedes the earlier statement. If the description of the offering varies between any free writing prospectus we have authorized for use in connection with this offering and this prospectus supplement, you should rely on the information in such free writing prospectus.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We have not authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. The information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein or therein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock or pre-funded warrants. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled “Where You Can Find More Information” and “Incorporation of Certain Information by Reference” in this prospectus supplement and in the accompanying prospectus.

We are offering to sell, and seeking offers to buy, shares of our common stock and pre-funded warrants only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock and pre-funded warrants in certain jurisdictions

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may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and pre-funded warrants and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless the context indicates otherwise, as used in this prospectus supplement, unless the context otherwise requires, references to “we,” “us,” “our,” “the company” and “Taysha” refer to Taysha Gene Therapies, Inc.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein contain forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein include, among other things, statements about:

- 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, or IND, and Clinical Trial Agreement submissions, initiation of clinical trials and timing of expected clinical results for TSHA-102 for Rett syndrome 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;
- any potential exercise by Audentes Therapeutics, Inc. (d/b/a Astellas Gene Therapy), or Astellas, of the options granted to Astellas pursuant to the Option Agreement dated October 21, 2022 by and between us and Astellas, or the Option Agreement, and our plans and expectations regarding our obligations and performance under the Option Agreement;
- 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 process 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 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;
- the costs of litigation and our expectations regarding the outcome of lawsuits and other claims against us and any regulatory or legal proceedings;
- our ability to identify, recruit and retain key personnel;

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- 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 competitive position and the development of and projections relating to our competitors or our industry;
- our financial performance;
- our estimates regarding cash runway, future revenue, expenses and needs for additional financing;
- our expectations regarding the time during which we will be an emerging growth company under the Jumpstart Our Business Startups Act of 2012, or the JOBS Act; and
- our intended use of proceeds from this offering.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this prospectus supplement, particularly in the “Risk Factors” section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained elsewhere in this prospectus supplement and the accompanying 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 supplement and the accompanying prospectus carefully, especially the risks of investing in our common stock discussed under “Risk Factors” beginning on page S-14 of this prospectus supplement and under a similar heading in our Annual Report on Form 10-K for the year ended December 31, 2024, or the 2024 Form 10-K, and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2025, or the First Quarter 2025 Form 10-Q, each of which is incorporated by reference in this prospectus supplement, along with our financial statements and notes to those financial statements and the other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision.

Company Overview

We are a clinical-stage biotechnology company focused on advancing AAV-based gene therapies for the treatment of severe monogenic diseases of the central nervous system, or CNS. Our lead clinical program TSHA-102 is in development for the treatment of Rett syndrome, a rare neurodevelopmental disorder with no approved disease-modifying therapies that address the genetic root cause of the disease. With a singular focus on developing transformative medicines, we aim to address severe unmet medical needs and dramatically improve the lives of patients and their caregivers. Our management team has proven experience in gene therapy development and commercialization. We leverage this experience, our manufacturing process and a clinically and commercially proven AAV9 capsid in an effort to rapidly translate treatments from bench to bedside.

We are evaluating TSHA-102 in the REVEAL Phase 1/2 adolescent and adult trial, which is a first-in-human, open-label, randomized, dose-escalation and dose-expansion study evaluating the safety and preliminary efficacy of TSHA-102 as a single lumbar intrathecal administration in adolescent and adult females aged 12 years and older with Rett syndrome due to MECP2 loss-of-function mutation. The trial is taking place in Canada and the United States. We are also evaluating TSHA-102 in the REVEAL Phase 1/2 pediatric trial, which is an open-label, randomized, dose-escalation and dose-expansion study evaluating the safety and preliminary efficacy of TSHA-102 as a single lumbar intrathecal administration in pediatric females with Rett syndrome due to MECP2 loss-of-function mutation. The trial is taking place in the United States, Canada and the United Kingdom.

We have received orphan drug designation and rare pediatric disease designation from the United States Food and Drug Administration, or the FDA, and orphan drug designation from the European Commission for TSHA-102 for the treatment of Rett syndrome. We also received Fast Track Designation from the FDA for TSHA-102 for the treatment of Rett syndrome. We also received Clinical Trial Authorisation, or CTA, clearance from the United Kingdom’s Medicines and Healthcare Products Regulatory Agency, or U.K. MHRA, in early 2024 for pediatric patients with Rett syndrome. In February 2024, we received Innovative Licensing and Access Pathway, or ILAP, designation for TSHA-102 from the U.K. MHRA. The ILAP aims to facilitate patient access to novel treatments by accelerating time to market through opportunities for enhanced engagements with U.K. regulatory authorities and other stakeholders. In April 2024, the FDA granted Regenerative Medicine Advanced Therapy, or RMAT, designation for TSHA-102 in Rett syndrome following the FDA’s review of available safety and efficacy data from the first three patients with Rett syndrome dosed with the low dose of TSHA-102 (5.7×10^{14} total vg) across the REVEAL Phase 1/2 adolescent and adult trial and the REVEAL Phase 1/2 pediatric trial.

Our Pipeline

We are focused on discovering, developing and commercializing gene therapies for the treatment of monogenic diseases of the CNS, in both rare and large patient populations. Our primary focus is advancing our lead TSHA-102

clinical program in Rett syndrome, while our pipeline of CNS programs offers the potential for additional development opportunities in the future. The stage of development of our Rett syndrome program, including the progress in our ongoing clinical trials, is represented in the table below:



Recent Developments

Clinical and Regulatory Update on TSHA-102

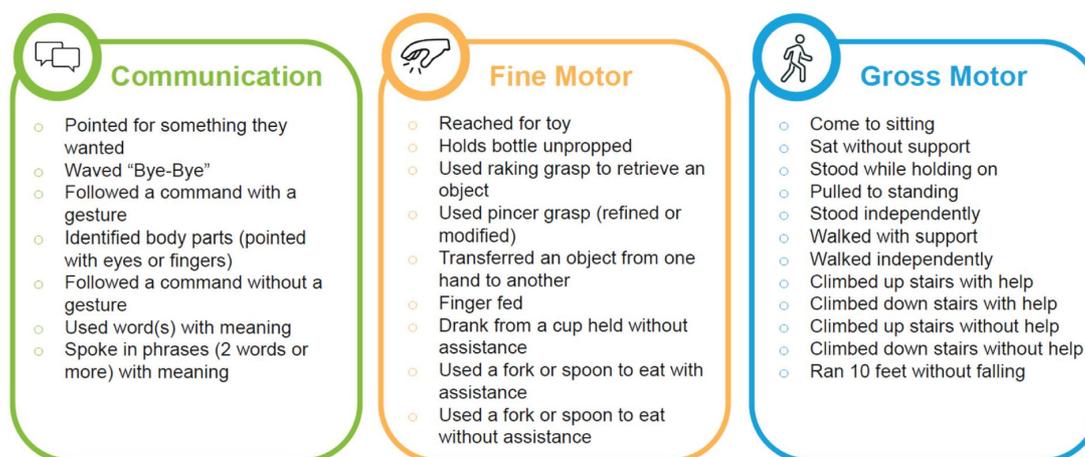
On May 28, 2025, we announced new clinical data from Part A of the REVEAL Phase 1/2 adolescent/adult and pediatric trials evaluating TSHA-102 in Rett syndrome, as well as key elements of the planned pivotal Part B trial design for its TSHA-102 program following written alignment from the FDA. The alignment reached with the FDA was supported by our analysis of the longitudinal Rett syndrome natural history study, or NHS, data from the International Rett Syndrome Foundation, or IRSF, as well as clinical data from the ongoing REVEAL Phase 1/2 trials.

Natural History Study

The NHS dataset from the IRSF contains clinical data from approximately 1,100 females with confirmed Rett syndrome diagnosis and has up to 14 years of follow-up data. The NHS captures longitudinal data examining the gain, loss, and regain of developmental milestones across core functional domains of Rett syndrome: communication, fine motor function and gross motor function. According to independent third-party caregiver research, these functional skills and activities of daily living are highly important to caregivers.

We leveraged a cohort of approximately 1,100 females with up to 14 years of follow up that met our REVEAL trial criteria to develop age- and time-based cumulative incidence curves that demonstrate the incidence of gaining a new milestone. The cumulative incidence models demonstrated distinct age-and time-based trends in developmental milestone acquisition that strengthened our understanding of the longitudinal disease progression in Rett syndrome and substantiated the disease-modifying potential of TSHA-102 and informed our discussions with the FDA on the proposed pivotal trial design.

We identified 28 developmental milestones from the NHS dataset that would reflect meaningful functional gains to caregivers and represent or are closely linked to activities of daily living that, based on our cumulative incidence models of the NHS data, demonstrate an approximate 0% likelihood of being achieved at the age of six years and older if a patient does not receive treatment. The 28 developmental milestones are depicted in the chart below:



The NHS cumulative incidence models demonstrated that patients of six years of age or greater have reached a developmental plateau, with an exceedingly low (ranging from 0% to <6.7%) likelihood of gaining new developmental milestones and regaining developmental milestones that were lost after a defined number of years. We leveraged these findings to establish the developmental plateau population of patients who are six or more years of age.

These models of developmental milestone NHS data informed our discussion with the FDA on our proposed pivotal trial design for TSHA-102. We believe the NHS models provide a data-driven, objective approach to assessing functional gains in a single-arm trial.

Regulatory Update and Pivotal Part B Trial Design

We have obtained written alignment from the FDA on key elements of our pivotal Part B REVEAL clinical trial design following formal discussions enabled by the Regenerative Medicine Advanced Therapy, or RMAT, mechanism. The clinical trial is planned as a single-arm, open-label pivotal trial with each patient serving as their own control. We intend to enroll 15 female patients in the developmental plateau population of Rett syndrome (≥ 6 years) with the intended dose of 1×10^{15} total vg, which is the high dose in Part A. The primary endpoints will assess developmental milestone gain or regain. During advanced discussions with the FDA, we reached alignment on the definition of a responder: the gain or regain of one or more of the defined developmental milestones. The FDA also provided guidance on an additional analysis to further support the responder definition. We have completed the analysis and intend to submit it alongside the final protocol and statistical analysis plan, or SAP, including sample size, responder rate and interim analysis, as part of the Investigational New Drug, or IND, amendment described below. As part of the pivotal Part B trial, video-based determination of milestone gain/regain will be performed by independent, blinded central raters according to predefined definitions of achievement for each developmental milestone.

We will also be conducting a separate safety study of TSHA-102 in females in the pre-developmental plateau population (2-6 years), and efficacy data will be extrapolated from the developmental plateau population. In the pivotal Part B trial, we plan to perform a 12-month primary analysis and a six-month interim analysis. The FDA

advised us to submit the pivotal Part B trial protocol and the associated SAP as an amendment to the IND application. We expect to submit the pivotal trial protocol and SAP amendment in the second quarter of 2025.

Clinical Data from Part A of Ongoing REVEAL Phase 1/2 Adolescent/Adult and Pediatric Trials

The clinical trial efficacy data is based on the May 19, 2025 data cutoff, and included a total of 10 females with Rett syndrome (high dose, N=6; low dose, N=4) aged 6-21 years at dosing treated with the high dose (1×10^{15} total vg) or low dose (5.7×10^{14} total vg) of TSHA-102. In both clinical trials, 100% of the pediatric, adolescent and adult patients gained or regained one or more defined developmental milestone across the core functional domains of communication, fine motor function, and gross motor function post-TSHA-102 administration, with an approximately 0% likelihood of being achieved without treatment based on natural history data. The developmental milestone gains and regains were determined by multiple independent, central raters, who evaluated functional skills through video evidence at baseline and post-treatment, against predefined binary criteria.

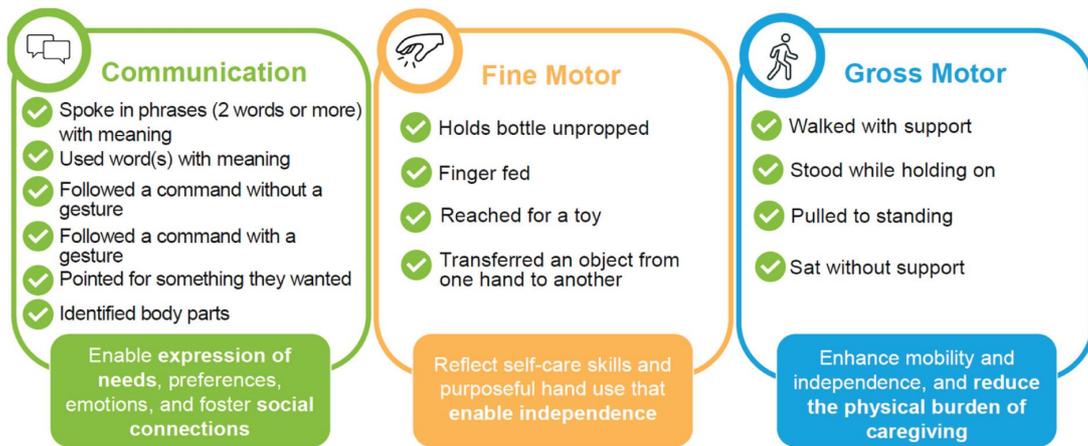
Milestones achieved post TSHA-102 treatment for all 10 patients are depicted in the chart below:

	Cohort 1: Low Dose 5.7×10^{14} total vg				Cohort 2: High Dose 1×10^{15} total vg					
AGE AT DOSING (years):	20	21	6	7	15	21	16	8	6	7
POST-TREATMENT FOLLOW UP:	18 mos.	18 mos.	12 mos.	12 mos.	9 mos.	9 mos.	6 mos.	6 mos.	6 mos.	3 mos.
	Developmental Milestone Gained Post-TSHA-102				Developmental Milestone Gained Post-TSHA-102					

Developmental milestone gains and regains were assessed by multiple independent central raters, who evaluated functional skills through video evidence at baseline and post-treatment, applying predefined binary criteria.

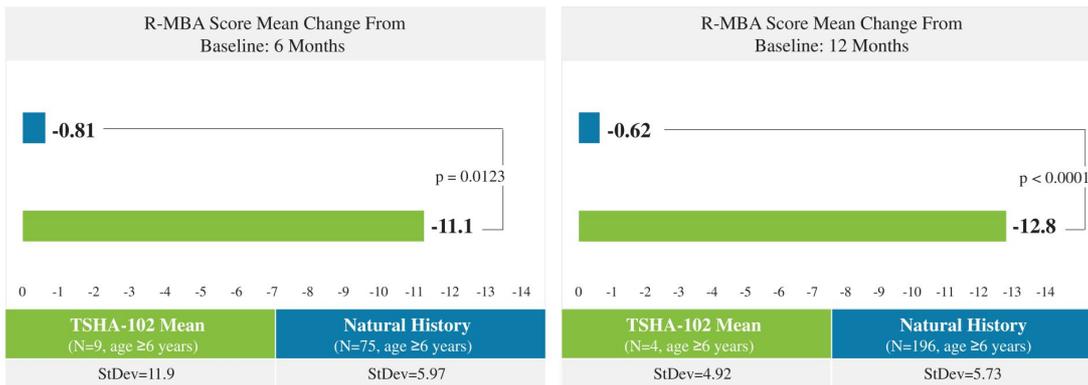
A total of 22 developmental milestones were achieved across the 10 patients. Developmental milestones were achieved early post-TSHA-102 administration, with new gains/regains demonstrated over time. The high dose cohort achieved a 100% responder rate 25% faster than the low dose cohort, supporting the accelerated functional benefit observed with the high dose.

A summary of the developmental milestones that were gained or regained in the REVEAL trials across the core functional domains of Rett syndrome post-TSHA-102 treatment is summarized in the chart below:



The high dose cohort consistently outperformed the low dose cohort in Part A of the REVEAL trials across multiple outcome measures. Specifically, improvements were observed across multiple clinician-assessed outcome measures, including Revised Motor Behavior Assessment, or R-MBA, and Clinician Global Impression – Improvement, or CGI-I, which corroborated the developmental milestone gains/regains demonstrated post-TSHA-102.

Patients demonstrated a statistically significant mean R-MBA score improvement post-TSHA-102 administration compared to natural history data at both six- and 12-months post-treatment. The improvement in R-MBA score at six- and 12-months post-treatment is depicted in the graphs below:



TSHA-102 also demonstrated early global improvement, with dose-dependent effects deepening over time, in CGI-I. The high dose cohort consistently outperformed the low dose cohort in CGI-I at the comparable time points of three months, six months and nine months post-treatment. The CGI-I score improvement for both cohorts are summarized in the below table:

Low Dose: Average CGI-I Score	3.0 <small>(N=4)</small>	2.3 <small>(N=4)</small>	3.0 <small>(N=2)</small>	3.3 <small>(N=4)</small>	2.0 <small>(N=2)</small>
High Dose: Average CGI-I Score	2.7 <small>(N=6)</small>	2.0 <small>(N=5)</small>	1.0 <small>(N=2)</small>		
Time Post TSHA-102:	3 months	6 months	9 months	12 months	18 months

The high dose cohort continually outperformed the low dose cohort across key outcome measures six months post-treatment, with dose-dependent effects deepening over time at nine months or greater post-treatment. A summary of the dose-dependent effects is depicted in the chart below:

Endpoint		Low Dose Cohort	High Dose Cohort	Dose-dependent Response?
Developmental Milestones	Responder Rate (%)	100% by 12 months	100% by 9 months	
	Responder Rate at 6 Months (%)	75%	83%	
R-MBA¹	Patients with R-MBA Improvement (%) at latest visit	100%	100%	
	Mean Score Improvement at 6 Months	-9.8	-12.2	
	Mean Score Improvement at ≥9 Months	-11.5	-18.0	
CGI-I	Patients with CGI-I Improvement (%) at latest visit	75%	100%	
	Mean CGI-I Score at 6 Months	2.3	2.0	
	Mean CGI-I Score at ≥9 Months	2.8	1.0	
CGI-S	Patients with CGI-S Improvement (%) at latest visit	25%	33%	

¹ R-MBA mean score change post-TSHA-102 is relative to baseline; lower score=improvement from baseline

In both the high dose and low dose cohorts of the TSHA-102 REVEAL clinical trials, TSHA-102 was generally well tolerated with no treatment-related serious adverse events, or SAEs, or dose limiting toxicities, or DLTs, as of the May 20, 2025 data cutoff for 12 patients aged 6-21 years (high dose, N=8; low dose, N=4). The treatment-emergent adverse events, or AEs, related to TSHA-102 were mild to moderate in severity. In addition, seizures have generally been well controlled following TSHA-102 administration. The number of adverse events across 12 pediatric, adolescent and adult patients is summarized in the table below:

Number of Events Across 12 Pediatric, Adolescent and Adult Patients Dosed in Part A of REVEAL Phase 1/2 Trials						
	Low Dose 5.7x10 ¹⁴ vg (N=4)		High Dose 1x10 ¹⁵ vg (N=8)		Total (N=12)	
	N	E	N	E	N	E
TEAE Related to TSHA-102:	4	[10]	5	[14]	9	[24]
Serious TEAE Unrelated to TSHA-102:	2	[7]	4	[6]	6	[13]
Serious TEAE Related to TSHA-102:	0	0	0	0	0	0

*Includes the following: hepatic enzyme increased, hypertransaminasemia, transaminases increased, and liver function test increased

- All treatment emergent adverse events, or TEAEs, related to TSHA-102 were mild-moderate in severity, with the most common being elevated liver enzymes* (N=4, 33%), pyrexia (N=3, 25%), lethargy (N=2, 17%), and elevated levels of neurofilament light protein in cerebrospinal fluid, (clinically insignificant) (N=2, 17%)
- Expected transaminase elevations observed
 - Majority experience mild elevations <2x upper limit of normal (ULN)
 - Acute excursions (>5x ULN) less common, clinically asymptomatic and steroid treatment-responsive
- Seizures have generally been well controlled following TSHA-102

Astellas: Rett Option Period

In October 2022, we entered into an Option Agreement with Audentes Therapeutics, Inc. (d/b/a Astellas Gene Therapy), or Astellas. Pursuant to the Option Agreement, we granted to Astellas an exclusive option to an exclusive license of certain rights related to TSHA-102, or the Rett Option. Subject to certain limited extensions, Astellas may exercise the Rett Option through a specified period of time, or the Rett Option Period, following Astellas’ receipt of certain clinical data from the female pediatric trial, or the Rett Data Package. We expect to deliver the Rett Data Package to Astellas in mid-2025. Under the Option Agreement, Astellas must decide whether to exercise the Rett Option within 90 days after Astellas’ receipt of the Rett Data Package, which would then trigger a good faith negotiation period further described in “—Option Agreement with Astellas” below. We are substantially dependent on TSHA-102, which is our sole product candidate, and we believe that if Astellas exercises the Rett Option, it would constitute an offer for the sale of substantially all of the assets of our company, which would result in a change of control requiring stockholder approval.

It is possible that Astellas will not exercise the Rett Option. If Astellas does exercise the Rett Option, Astellas may not agree with our assessment that the exercise of the Rett Option for the exclusive license of TSHA-102 would result in a change of control, and we cannot predict whether or how the parties would resolve such dispute. See “—Option Agreement with Astellas” and “Risk Factors—We are substantially dependent on the success of our lead product candidate, TSHA-102. There is no guarantee that we will be able to successfully develop and commercialize TSHA-102. If we are unable to complete development of, obtain regulatory approval for and commercialize TSHA-102 in one or more indications and in a timely manner, our business, financial condition, results of operations and prospects will be significantly harmed.”

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.
- 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.
- Interim “top-line” and preliminary results from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.
- We have not yet completed testing of any product candidate in clinical trials. Success in preclinical studies or earlier clinical trials, including our Phase 1/2 REVEAL trials of TSHA-102, may not be indicative of results in future clinical trials, or provide support for the submission of a marketing application.
- As an organization, we have never conducted pivotal clinical trials, and may be unable to do so for any product candidates we may develop, including TSHA-102.
- We are substantially dependent on the success of our lead product candidate, TSHA-102. There is no guarantee that we will be able to successfully develop and commercialize TSHA-102. If we are unable to complete development of, obtain regulatory approval for and commercialize TSHA-102 in one or more indications and in a timely manner, our business, financial condition, results of operations and prospects will be significantly 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 FDA, European Medicines Agency 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.
- Healthcare legislative or regulatory reform measures may have a negative impact on our business and results of operations.
- We may not be successful in our efforts to build a pipeline of additional product candidates or our next-generation platform technologies.
- Unfavorable conditions in our industry or the global economy could limit our ability to grow our business and negatively affect our results of operations.
- 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.
- We are subject to legal proceedings and claims from time to time that may seek material damages or otherwise may have a material adverse effect on our business. The costs we incur in defending ourselves or associated with settling any of these proceedings, as well as a material final judgment or decree against us, could materially adversely affect our financial condition. 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.
- Raising additional capital, including as a result of this offering, may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our product candidates.
- If you purchase shares of common stock or pre-funded warrants in this offering, you will suffer immediate dilution of your investment.
- We have broad discretion over the use of our cash and cash equivalents, including the net proceeds we receive in this offering, and may not use them effectively.

Option Agreement with Astellas

Under the Option Agreement, we granted to Astellas the Rett Option, which is an exclusive option to obtain an exclusive, worldwide, royalty and milestone-bearing right related to TSHA-102. Subject to certain extensions, the Rett Option is exercisable for 90 days after Astellas' receipt of the Rett Data Package in mid-2025. The parties have agreed that, if Astellas exercises the Rett Option, the parties would, for a period of 130 days, negotiate a license agreement in good faith on the terms and conditions outlined in the Option Agreement. If the parties were unable to mutually agree on such terms within 120 days, the terms of such license agreement may, at Astellas' discretion, be determined by "baseball arbitration," wherein each party is required to submit a proposed final license agreement to the arbitrators, and the arbitrators are required to select one of the proposed license agreements without modification.

Under the Option Agreement, we have agreed that if, during the Rett Option Period, Astellas submits an offer for a transaction that would result in a change of control of our company, we will negotiate with Astellas in good

faith the potential terms and conditions of such a transaction for 45 days. If we are unable to mutually agree on such terms, such right of first offer will expire. In addition, we have agreed during the Rett Option Period 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, 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. During the Rett Option Period, we may not enter into (a) any letter of intent, agreement, contract or commitment (whether or not binding) with respect to a change of control or (b) any agreement, contract or commitment that could impede the ability of Astellas to effect a change of control, or a Competing Instrument, unless we promptly notify Astellas, in writing, within a specified period before entering into a Competing Instrument.

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 supplement. We have included our website in this prospectus supplement 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 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 supplement. 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 supplement 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 us	46,868,687 shares
Pre-funded warrants offered by us	We are also offering, in lieu of common stock to certain investors that so choose, pre-funded warrants to purchase up to 25,858,586 shares of our common stock. The purchase price of each pre-funded warrant will equal the price per share at which the shares of our common stock are being sold to the public in this offering, minus \$0.001, which is the exercise price of each pre-funded warrant per share. Each pre-funded warrant will be exercisable at any time after the date of issuance of such pre-funded warrant, subject to an ownership limitation. See “Description of the Pre-Funded Warrants” on page S-23 of this prospectus supplement. This prospectus supplement also relates to the offering of the shares of our common stock issuable upon exercise of the pre-funded warrants.
Underwriters’ option to purchase additional shares	10,909,090 shares
Common stock to be outstanding immediately after this offering	251,923,257 shares (or 262,832,347 shares if the underwriters exercise in full their option to purchase additional shares), assuming no exercise of any pre-funded warrants issued in this offering.
Use of proceeds	<p>We estimate that the net proceeds from this offering will be approximately \$187.4 million (or approximately \$215.6 million if the underwriters exercise in full their option to purchase up to 10,909,090 additional shares of common stock), assuming a public offering price of \$2.75 per share and \$2.749 per pre-funded warrant, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. These estimates exclude the nominal proceeds, if any, from the exercise of the pre-funded warrants sold in this offering.</p> <p>We currently intend to use the net proceeds from this offering, together with our current cash and cash equivalents, to fund clinical, regulatory and manufacturing development for TSHA-102 in Rett syndrome and general working capital purposes. See the section titled “Use of Proceeds” beginning on page S-20 for additional information.</p>
Risk factors	You should read the “Risk Factors” section of this prospectus supplement beginning on page S-14 and page 6 of the accompanying prospectus, respectively, and the “Risk Factors” section in our 2024 Form 10-K and our First Quarter 2025 Form 10-Q, respectively, each of which is incorporated by reference, for a discussion of factors to consider carefully before deciding to invest in our securities.
Nasdaq Global Select Market symbol	Our common stock is listed on The Nasdaq Global Select Market under the symbol “TSHA”. We do not intend to apply for listing of

the pre-funded warrants on The Nasdaq Global Select Market or any securities exchange or nationally recognized trading system.

The number of shares of our common stock to be outstanding after this offering is based on 205,054,570 shares of our common stock outstanding as of March 31, 2025, and excludes:

- 24,326,199 shares of our common stock issuable upon the exercise of stock options outstanding as of March 31, 2025, at a weighted average exercise price of \$2.72 per share;
- 1,049,338 shares of common stock issuable upon the settlement of vested restricted stock units outstanding as of March 31, 2025;
- 6,241,566 shares of common stock issuable upon the vesting of restricted stock units outstanding as of March 31, 2025;
- 63,223,199 shares of common stock issuable upon the exercise of outstanding pre-funded warrants to purchase shares of common stock outstanding as of March 31, 2025 with an exercise price of \$0.001 per share;
- 316,667 shares of common stock issuable upon the exercise of outstanding common warrants to purchase shares of common stock outstanding as of March 31, 2025 with an exercise price of \$0.7090 per share;
- 2,213,188 shares of common stock reserved for future issuance under our 2020 Stock Incentive Plan as of March 31, 2025;
- 2,533,125 shares of our common stock reserved for future issuance under our 2020 Employee Stock Purchase Plan as of March 31, 2025; and
- 2,492,607 shares of our common stock reserved for future issuance under our 2023 Inducement Plan as of March 31, 2025.

Unless otherwise indicated, all information in this prospectus supplement assumes (i) no exercise of the outstanding options or settlement of unvested restricted stock units described above, (ii) no exercise of outstanding pre-funded warrants or common warrants described above, (iii) no exercise by the underwriters of their option to purchase additional shares of our common stock and (iv) no exercise of the pre-funded warrants offered and sold in this offering.

RISK FACTORS

Investing in our common stock involves a high degree of risk. Before you decide to invest in our common stock, you should carefully consider the risks and uncertainties described below together with all other information contained in this prospectus supplement, the accompanying prospectus and in our filings with the SEC that we have incorporated by reference in this prospectus supplement and the accompanying prospectus. The risk factors included in this prospectus supplement update the corresponding risk factors incorporated by reference in this prospectus supplement from our 2024 Form 10-K and our First Quarter 2025 Form 10-Q. If any of the following risks or any of the risks incorporated herein by reference actually occurs, our business, prospects, operating results and financial condition could suffer materially. In such event, the trading price of our common stock could decline and you might lose all or part of your investment.

Risks Related to the Development of TSHA-102

Interim “top-line” and preliminary results from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publish interim top-line or preliminary results from our clinical trials. Interim results from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Preliminary or top-line results also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, interim and preliminary data should be viewed with caution until the final data are available. For example, in May 2025, we announced clinical data from adult/adolescent and pediatric patients treated in the Phase 1/2 REVEAL trials of TSHA-102. However, those observations may not endure as patients continue their follow-up visits as part of the trial. Initial clinical observations also may not translate into success on primary endpoints of the REVEAL trial. Differences between preliminary or interim data and final data could significantly harm our business prospects and may cause the trading price of our common stock to fluctuate significantly.

Further, others, including regulatory authorities, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the approvability or commercialization of the particular product candidate or product and our business in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular drug, product candidate or our business. If the top-line data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for and commercialize any of our product candidates, our business, operating results, prospects or financial condition may be harmed.

We are substantially dependent on the success of our lead product candidate, TSHA-102. There is no guarantee that we will be able to successfully develop and commercialize TSHA-102. If we are unable to complete development of, obtain regulatory approval for and commercialize TSHA-102 in one or more indications and in a timely manner, our business, financial condition, results of operations and prospects will be significantly harmed.

We are substantially dependent on the success of our lead product candidate, TSHA-102, which is currently our sole product candidate in clinical development. We are still developing TSHA-102 and it cannot be marketed or sold in the United States or in foreign markets until regulatory approval has been obtained from the FDA or applicable foreign regulatory agencies. The process of obtaining regulatory approval is expensive and time

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consuming. The FDA and foreign regulatory authorities may never approve TSHA-102 for sale and marketing, and even if TSHA-102 is ultimately approved, regulatory approval may be delayed or limited in the United States or in other jurisdictions. Even if we are authorized to sell and market TSHA-102 in one or more markets, there is no assurance that we will be able to successfully market TSHA-102 or that TSHA-102 will achieve market acceptance sufficient to generate profits. If we are unable to successfully develop and commercialize TSHA-102 due to failure to obtain regulatory approval for TSHA-102, to successfully market TSHA-102, to generate profits from the sale of TSHA-102, or due to other risk factors outlined in this report, it would have material adverse effects on our business, financial condition, and results of operations.

In October 2022, we entered into the Option Agreement, pursuant to which we granted the Rett Option to Astellas. Subject to certain limited extensions, Astellas may exercise the Rett Option through the Rett Option Period, following Astellas' receipt of the Rett Data Package. We expect to deliver the Rett Data Package to Astellas in mid-2025. Under the Option Agreement, Astellas must decide whether to exercise the Rett Option within 90 days after Astellas' receipt of the Rett Data Package, which would then trigger a good faith negotiation period, as further described in "Prospectus Summary—Option Agreement with Astellas." Under the Option Agreement, we also granted to Astellas certain rights with respect to a change of control of our company during the Rett Option Period, as discussed in "Prospectus Summary—Option Agreement with Astellas." These rights include, but are not limited to, a right of first offer in the event that we receive an offer or proposal from a third party that would result in a change of control, and 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, 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. In addition, we have agreed that if, during the Rett Option Period, Astellas submits an offer for a transaction that would result in a change of control of our company, we will negotiate with Astellas in good faith the potential terms and conditions of such a transaction for 45 days. If we are unable to mutually agree on such terms, such right of first offer will expire.

Because we are substantially dependent on TSHA-102, which is our sole product candidate in clinical development, we believe that if Astellas exercises the Rett Option, such exclusive license of TSHA-102 would constitute a sale of substantially all of the assets of our company, which would result in a change of control requiring stockholder approval. It is possible that Astellas will not exercise the Rett Option. If Astellas does exercise the Rett Option, Astellas may not agree with our assessment that the exercise of the Rett Option for the exclusive license of TSHA-102 would result in a change of control, and we cannot predict whether or how the parties would resolve such dispute. While it is inherently difficult to assess the potential outcome of any such dispute, we may be exposed to additional risks as a result, including, but not limited to, reputational harm and litigation, and we can provide no assurances that we will prevail in any such litigation. If Astellas exercises the Rett option and it were determined that such exclusive license does not constitute a sale of substantially all of the assets of our company, and the exercise of the Rett Option is not an offer that would result in a change of control, under the Option Agreement, the parties are obligated to negotiate the terms of the license agreement in good faith for a period of 130 days. If the parties are unable to mutually agree on such terms within 120 days, the terms of such license agreement may, at Astellas' discretion, be determined by "baseball arbitration," wherein each party is required to submit a proposed final license agreement to the arbitrators, and the arbitrators are required to select one of the proposed license agreements without modification. Given our substantial reliance on TSHA-102, if we enter into a license agreement for TSHA-102 and we are unable to develop other product candidates at that time, it could have a material adverse effect on our business, financial condition, results of operations and prospects, including, but not limited to, the potential cessation of our operations or the need to begin development of any of our preclinical programs.

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We have not yet completed testing of any product candidate in clinical trials. Success in preclinical studies or earlier clinical trials, including our Phase 1/2 REVEAL trials of TSHA-102, may not be indicative of results in future clinical trials, or provide support for the submission of a marketing application.

Success in preclinical testing and early clinical trials does not ensure that later clinical trials will generate the same results or otherwise provide adequate data to demonstrate the efficacy and safety of a product candidate. Preclinical tests and Phase 1 and Phase 2 clinical trials are primarily designed to test safety, to study pharmacokinetics and pharmacodynamics and to understand the side effects of product candidates at various doses and schedules. Success in preclinical or animal studies and early clinical trials does not ensure that later large-scale efficacy trials will be successful nor does it predict final results. For example, we may be unable to identify suitable animal disease models for our product candidates, which could delay or frustrate our ability to proceed into clinical trials or obtain marketing approval. Our product candidates, including TSHA-102, may fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies or having successfully advanced through initial clinical trials. Any such outcome would cause us to cease development of TSHA-102, which is currently our only product candidate in clinical development. Our Phase 1/2 clinical trials of TSHA-102 involve small patient populations and duration of treatment has been relatively short. Because of the small sample sizes, the results of these trials may not be indicative of results of future clinical trials. Further, although other gene therapy clinical trials conducted by others also utilized AAV9 vectors, these trials should not be relied upon as evidence that our planned clinical trials will succeed.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including changes in regulatory policy during the period of our product candidate development. Any such delays could negatively impact our business, financial condition, results of operations and prospects.

As an organization, we have never conducted pivotal clinical trials, and may be unable to do so for any product candidates we may develop, including TSHA-102.

We will need to successfully complete our ongoing and planned clinical trials, including pivotal clinical trials, in order to obtain FDA and comparable foreign regulatory approval to market our product candidates. Carrying out later-stage clinical trials and the submission of a successful BLA and comparable foreign application is a complicated process. As an organization, we have initiated Phase 1/2 clinical trials, have not previously conducted any later stage or pivotal clinical trials, but have limited experience in preparing, submitting and prosecuting regulatory filings and have not previously submitted a BLA or comparable foreign application for any product candidate.

In addition, we have had limited interactions with the FDA and comparable foreign regulatory authorities and cannot be certain how many additional clinical trials of TSHA-102 will be required or how such trials should be designed. Although we have received feedback from the FDA on the design of Part B of our clinical trial of TSHA-102, there is no assurance that our trial design will be sufficient for FDA approval. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to BLA submission or comparable foreign application and approval of TSHA-102. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of TSHA-102. Failure to commence or complete, or delays in, our planned clinical trials, could prevent us from or delay us in commercializing TSHA-102.

Risks Related to Legal and Regulatory Compliance Matters

We are subject to legal proceedings and claims from time to time that may seek material damages or otherwise may have a material adverse effect on our business. The costs we incur in defending ourselves or associated with settling any of these proceedings, as well as a material final judgment or decree against us, could materially adversely affect our financial condition.

We are subject to legal proceedings and claims from time to time that may seek material damages or otherwise may have a material adverse effect on our business. For example, in January 2024 and April 2024, we were named a nominal defendant in stockholder derivative lawsuits asserting claims against certain of our current and former directors, among others, in the Court of Chancery of the State of Delaware. These lawsuits, which have since been consolidated, seek, among other relief, a declaration that certain defendants were unjustly enriched, unspecified monetary damages, disgorgement of certain alleged profits received by defendants, and reasonable costs and expenses, including attorneys' fees, and other relief. We have not recorded a liability related to these lawsuits because, at this time, we are unable to reasonably estimate possible losses or gains or determine whether an unfavorable outcome is either probable or remote. Our board of directors has formed a special litigation committee to investigate the claims and allegations in the amended complaint, which is ongoing. In connection with an investigation captioned In the Matter of Taysha Gene Therapies, Inc. (D-04192), we and certain of our officers and directors received subpoenas in late 2024 from the SEC for materials relating to our August 2023 PIPE and certain public offerings. The SEC investigation is neither a determination that the Company or any individuals have violated any law nor a charge of any wrongdoing. See "Item 3-Legal Proceedings" and "Part II, Item 8, Note 13-Commitments and Contingencies" in the 2024 Form 10-K for more information and "Part I, Item 2, Note 13-Commitments and Contingencies" in our First Quarter 2025 Form 10-Q for more information about each of these matters.

Due to the inherent uncertainties in legal proceedings, we cannot accurately predict the duration, scope or ultimate outcome of any such proceedings. This or any future litigation, regardless of the merits of any such proceeding, could harm our reputation and result in substantial costs and diversion of management's attention and resources, which could adversely impact our business. Although we have directors' and officers' liability insurance, it provides for a substantial retention of liability and is subject to limitations and may not cover a significant portion, or any, of the expenses or liabilities we may incur or be subject to in connection with these lawsuits or other litigation to which we are party. The costs we incur in defending ourselves or associated with settling such proceedings, as well as a material final judgment or decree against us, that are not covered by our directors' and officers' liability insurance could materially adversely affect our financial condition. In addition, additional lawsuits may be filed, the conclusion of which in a manner adverse to us and for which we incur substantial costs or damages not covered by our directors' and officers' liability insurance could have a material adverse effect on our financial condition and business.

Risks Related to this Offering

Raising additional capital, including as a result of this offering, may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our product candidates.

Until such time, if ever, as we can generate substantial revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings and license and collaboration agreements. To the extent that we raise additional capital through the sale of equity securities, including from this offering, or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may be required to relinquish valuable rights to our technologies, intellectual

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property, potential future revenue streams, or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements with third parties when needed, we may be required to delay, limit, reduce or terminate our product candidate development or future commercialization efforts or grant rights to third parties to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

If you purchase shares of common stock or pre-funded warrants in this offering, you will suffer immediate dilution of your investment.

The price of our common stock in this offering is substantially higher than the net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock or pre-funded warrants in this offering, you will pay a price per share that substantially exceeds our net tangible book value per share after this offering. To the extent outstanding options, common warrants or pre-funded warrants are exercised or restricted stock units are settled in shares of our common stock, you will incur further dilution. Based on a public offering price of \$2.75 per share and \$2.749 per pre-funded warrant, which equals the offering price per share of the common stock less the \$0.001 per share exercise price of each such pre-funded warrant (and excluding shares of common stock issued or any resulting accounting associated with the pre-funded warrants), you will experience immediate dilution of \$1.79 per share, representing the difference between our as adjusted net tangible book value per share after giving effect to this offering and the public offering price. Furthermore, if the pre-funded warrants are exercised, you will incur further dilution. For additional information on the dilution that you will experience immediately after this offering, see the section titled "Dilution."

We have broad discretion over the use of our cash and cash equivalents, including the net proceeds we receive in this offering, and may not use them effectively.

Our management has broad discretion to use our cash and cash equivalents, including the net proceeds we receive in this offering, to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have an adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use to fund operations, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value.

A sale of a substantial number of shares of our common stock may cause the price of our common stock to decline.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. If our stockholders sell, or the market perceives that our stockholders intend to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline significantly.

We cannot predict what effect, if any, sales of our shares in the public market or the availability of shares for sale will have on the market price of our common stock. However, future sales of substantial amounts of our common stock in the public market, including shares issued upon exercise of outstanding options or warrants, or the perception that such sales may occur, could adversely affect the market price of our common stock.

In addition, Jefferies LLC, BofA Securities, Inc., Piper Sandler & Co. and Barclays Capital Inc. may, in their sole discretion, release all or some portion of the shares subject to the lock-up agreements associated with this offering at any time and for any reason. Sales of a substantial number of such shares upon expiration of the lock-up and market stand-off agreements, the perception that such sales may occur, or early release of these agreements, could cause our market price to fall or make it more difficult for you to sell your common stock at a time and price that you deem appropriate.

There is no public market for the pre-funded warrants being offered in this offering.

There is no public trading market for the pre-funded warrants being offered in this offering, and we do not expect a market to develop. In addition, we do not intend to apply to list the pre-funded warrants on any securities exchange or nationally recognized trading system, including The Nasdaq Global Select Market. Without an active market, the liquidity of the pre-funded warrants will be limited.

We will not receive a significant amount, or potentially any, additional funds upon the exercise of the pre-funded warrants; however, any exercise would increase the number of shares eligible for future resale in the public market and result in dilution to our stockholders.

Each pre-funded warrant may be exercised by way of a cashless exercise, meaning that the holder may not pay a cash purchase price upon exercise, but instead would receive upon such exercise the net number of shares of our common stock determined according to the formula set forth in the pre-funded warrant. Accordingly, we may not receive any additional funds upon the exercise of the pre-funded warrants. Even if a pre-funded warrant is exercised for cash, we will not receive any meaningful additional funds upon the exercise of the pre-funded warrants. To the extent such pre-funded warrants are exercised, additional shares of common stock will be issued for nominal or no additional consideration, which will result in dilution to the then existing holders of our common stock and will increase the number of shares eligible for resale in the public market.

Holders of any pre-funded warrants purchased in this offering will have no rights as holders of our common stock with respect to the shares of common stock underlying such pre-funded warrants until such holders exercise their pre-funded warrants and acquire our common stock.

Until holders of pre-funded warrants acquire shares of our common stock upon exercise of the pre-funded warrants, holders of pre-funded warrants will have no rights with respect to the shares of our common stock underlying such pre-funded warrants including with respect to dividends and voting rights. Upon exercise of the pre-funded warrants, the holders will be entitled to exercise the rights of a holder of our common stock with respect to the shares of common stock underlying such pre-funded warrants only as to matters for which the record date occurs after the exercise date.

Significant holders or beneficial holders of our common stock may not be permitted to exercise pre-funded warrants that they hold.

A holder of a pre-funded warrant will not be entitled to exercise any portion of any pre-funded warrant which, upon giving effect to such exercise, would cause (i) the aggregate number of shares of our common stock beneficially owned by the holder (together with its affiliates) to exceed 4.99% or 9.99%, as the case may be, of the number of shares of our common stock outstanding immediately prior to or after giving effect to the exercise, or (ii) the combined voting power of our securities beneficially owned by the holder (together with its affiliates) to exceed 4.99% or 9.99%, as the case may be, of the combined voting power of all of our securities then outstanding immediately prior to or after giving effect to the exercise, as such percentage ownership is determined in accordance with the terms of the pre-funded warrants. Such percentage may be increased by the holder of the pre-funded warrant to any other percentage not in excess of 19.99% upon at least 61 days' prior notice from the holder to us. As a result, you may not be able to exercise your pre-funded warrants for shares of our common stock at a time when it would be financially beneficial for you to do so. In such circumstance you could seek to sell your pre-funded warrants to realize value, but you may be unable to do so in the absence of an established trading market for the pre-funded warrants.

USE OF PROCEEDS

As of March 31, 2025, we had cash and cash equivalents of \$116.6 million. We estimate that the net proceeds to us from this offering will be approximately \$187.4 million, or approximately \$215.6 million if the underwriters exercise in full their option to purchase up to 10,909,090 additional shares of common stock, based on the public offering price of \$2.75 per share and \$2.749 per pre-funded warrant, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. These estimates exclude the nominal proceeds, if any, from the exercise of the pre-funded warrants sold in this offering.

We currently intend to use the net proceeds from this offering, together with our current cash and cash equivalents, to fund clinical, regulatory and manufacturing development for TSHA-102 in Rett syndrome and general working capital purposes.

Our expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our product candidate development, the status of and results from clinical trials, as well as any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs.

As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering, and investors will be relying on the judgment of our management regarding the application of the net proceeds from this offering. The timing and amount of our actual expenditures will be based on many factors, including cash flows from operations and the anticipated growth of our business. Pending these uses, we expect to invest the net proceeds in short-term, interest bearing obligations, certificates of deposit or direct or guaranteed obligations of the United States. The goal with respect to the investment of these net proceeds is capital preservation and liquidity so that such funds are readily available to fund our operations.

Based on the planned use of proceeds described above, we believe that the net proceeds from this offering, together with our current cash and cash equivalents, will be sufficient to enable us to fund our operating expenses and capital expenditure requirements into 2028. We have based this estimate on assumptions that may prove to be incorrect, and we could use our available capital resources sooner than we currently expect.

DILUTION

If you invest in our common stock or pre-funded warrants in this offering, your interest will be diluted immediately to the extent of the difference between the public offering price per share or pre-funded warrant you will pay in this offering and the as adjusted net tangible book value per share of our common stock after this offering. Our historical net tangible book value as of March 31, 2025 was \$55.1 million, or \$0.27 per share of common stock. Historical net tangible book value per share represents the amount of our total tangible assets less total liabilities, divided by the number of shares of our common stock outstanding on March 31, 2025.

After giving effect to our issuance and sale of 46,868,687 shares of common stock in this offering at a public offering price of \$2.75 per share and pre-funded warrants to purchase up to 25,858,586 shares of our common stock at the public offering price of \$2.749 per pre-funded warrant (and excluding shares of common stock issued or any resulting accounting associated with the pre-funded warrants), and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us and excluding proceeds, if any, from the exercise of the pre-funded warrants issued pursuant to this offering or any resulting accounting associated with the pre-funded warrants, our as adjusted net tangible book value as of March 31, 2025 would have been \$242.5 million, or \$0.96 per share. This represents an immediate increase in as adjusted net tangible book value per share of \$0.69 to existing stockholders and immediate dilution of \$1.79 in as adjusted net tangible book value per share to new investors purchasing common stock in this offering. Dilution per share to new investors is determined by subtracting as adjusted net tangible book value per share after this offering from the public offering price per share paid by new investors. The following table illustrates this per share dilution to the new investors purchasing securities in this offering without giving effect to the option to purchase additional shares granted to the underwriters:

Public offering price per share (or pre-funded warrant in lieu thereof at the public offering price less \$0.001)	\$2.75
Net tangible book value per share as of March 31, 2025	\$0.27
Increase per share attributable to sale of shares of common stock and pre-funded warrants in this offering	<u>0.69</u>
As adjusted net tangible book value per share after this offering	<u>0.96</u>
Dilution per share to new investors	<u>\$1.79</u>

If the underwriters exercise their option to purchase 10,909,090 additional shares in full at the public offering price of \$2.75 per share, the as adjusted net tangible book value will increase to \$1.03 per share, representing an immediate increase to existing stockholders of \$0.76 per share and an immediate dilution of \$1.72 per share to new investors.

The above discussion and table are based on 205,054,570 shares of our common stock outstanding as of March 31, 2025, and excludes:

- 24,326,199 shares of our common stock issuable upon the exercise of stock options outstanding as of March 31, 2025, at a weighted average exercise price of \$2.72 per share;
- 1,049,338 shares of common stock issuable upon the settlement of vested restricted stock units outstanding as of March 31, 2025;
- 6,241,566 shares of common stock issuable upon the vesting of restricted stock units outstanding as of March 31, 2025;

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- 63,223,199 shares of common stock issuable upon the exercise of outstanding pre-funded warrants to purchase shares of common stock outstanding as of March 31, 2025 with an exercise price of \$0.001 per share;
- 316,667 shares of common stock issuable upon the exercise of outstanding common warrants to purchase shares of common stock outstanding as of March 31, 2025 with an exercise price of \$0.7090 per share;
- 2,213,188 shares of common stock reserved for future issuance under our 2020 Stock Incentive Plan as of March 31, 2025;
- 2,533,125 shares of our common stock reserved for future issuance under our 2020 Employee Stock Purchase Plan as of March 31, 2025; and
- 2,492,607 shares of our common stock reserved for future issuance under our 2023 Inducement Plan as of March 31, 2025.

If holders of the pre-funded warrants exercise the pre-funded warrants, the as adjusted net tangible book value per share after giving effect to this offering would be \$0.87 per share, representing an immediate increase to existing stockholders of \$0.60 per share, and immediate dilution to new investors in this offering of \$1.88 per share.

To the extent that any options, common warrants and pre-funded warrants are exercised, restricted stock units are settled in shares of our common stock, new stock awards are issued under our equity incentive plans or we otherwise issue additional shares of common stock in the future at a price less than the public offering price, there may be further dilution to new investors purchasing common stock in this offering.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock and provisions of our certificate of incorporation and bylaws are summaries. References to our certificate of incorporation herein refer to our certificate of incorporation as amended to the date of this prospectus supplement. You should also refer to the certificate of incorporation (including the certificate of amendment thereto) and the bylaws, which are filed as exhibits to our most recent Annual Report on Form 10-K and are incorporated by reference herein.

General

Our certificate of incorporation authorizes us to issue up to 400,000,000 shares of common stock, \$0.00001 par value per share, and 10,000,000 shares of preferred stock, \$0.00001 par value per share. Our board of directors may establish the rights and preferences of the preferred stock from time to time. As of March 31, 2025, we had outstanding 205,054,570 shares of common stock and no shares of preferred stock outstanding.

Common Stock

Voting Rights

Each holder of our common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors. The affirmative vote of holders of at least 66 2/3% of the voting power of all of the then-outstanding shares of capital stock, voting as a single class, is required to amend certain provisions of our certificate of incorporation, including provisions relating to amending the Company's bylaws, the classified board, the size of the Company's board, removal of directors, director liability, vacancies on the Company's board, special meetings, stockholder notices, actions by written consent and exclusive forum.

Dividends

Subject to preferences that may be applicable to any then-outstanding preferred stock, holders of common stock are entitled to receive ratably those dividends, if any, as may be declared from time to time by the board of directors out of legally available funds.

Liquidation

In the event of our liquidation, dissolution or winding up, holders of common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then-outstanding shares of preferred stock.

Rights and Preferences

Holders of common stock have no preemptive, conversion or subscription rights and there are no redemption or sinking fund provisions applicable to the common stock. The rights, preferences and privileges of the holders of common stock are subject to, and may be adversely affected by, the right of the holders of shares of any series of preferred stock that we may designate in the future.

Preferred Stock

Pursuant to our certificate of incorporation, our board of directors has the authority, without further action by our stockholders, from time to time, to designate and issue up to 10,000,000 shares of preferred stock in one or more series, to establish from time to time the number of shares to be included in each such series, to fix the rights, preferences and privileges of the shares of each wholly unissued series and any qualifications, limitations or

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restrictions thereon, and to increase or decrease the number of shares of any such series, but not below the number of shares of such series then outstanding. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of our common stock. The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in control of us and may adversely affect the market price of our common stock and the voting and other rights of the holders of our common stock.

Our board of directors will fix the designations, voting powers, preferences and rights of each series, as well as the qualifications, limitations or restrictions thereof, of the preferred stock of each series that we offer under this prospectus and applicable prospectus supplements in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of that series of preferred stock. This description will include:

- the title and stated value;
- the number of shares we are offering;
- the liquidation preference per share;
- the purchase price per share;
- the dividend rate per share, dividend period and payment dates and method of calculation for dividends;
- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- our right, if any, to defer payment of dividends and the maximum length of any such deferral period;
- the procedures for any auction and remarketing, if any;
- the provisions for a sinking fund, if any;
- the provisions for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;
- any listing of the preferred stock on any securities exchange or market;
- whether the preferred stock will be convertible into our common stock or other securities of ours, including depositary shares and warrants, and, if applicable, the conversion period, the conversion price, or how it will be calculated, and under what circumstances it may be adjusted;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange period, the exchange price, or how it will be calculated, and under what circumstances it may be adjusted;
- voting rights, if any, of the preferred stock;
- preemption rights, if any;
- restrictions on transfer, sale or other assignment, if any;
- whether interests in the preferred stock will be represented by depositary shares;
- a discussion of any material or special U.S. federal income tax considerations applicable to the preferred stock;

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- the relative ranking and preferences of the preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs;
- any limitations on issuances of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock being issued as to dividend rights and rights if we liquidate, dissolve or wind up our affairs; and
- any other specific terms, rights, preferences, privileges, qualifications or restrictions of the preferred stock.

The General Corporation Law of the State of Delaware, or DGCL, the state of our incorporation, provides that the holders of preferred stock will have the right to vote separately as a class (or, in some cases, as a series) on an amendment to our certificate of incorporation if the amendment would change the par value or, unless the certificate of incorporation provided otherwise, the number of authorized shares of the class or change the powers, preferences or special rights of the class or series so as to adversely affect the class or series, as the case may be. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

The issuance of preferred stock could adversely affect the voting power of holders of common stock and reduce the likelihood that common stockholders will receive dividend payments and payments upon liquidation. The issuance could have the effect of decreasing the market price of the common stock. The issuance of preferred stock also could have the effect of delaying, deterring or preventing a change in control of us.

Registration Rights

Astellas Registration Rights

In October 2022, we entered into a registration rights agreement, or the Astellas Registration Rights Agreement, with Astellas, pursuant to which we agreed to register the resale of 7,266,342 shares of our common stock issued and sold to Astellas in a private placement, or the Astellas Shares. We agreed to use reasonable best efforts 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.

In the event sales cannot be made pursuant to the registration statement, subject to certain limited exceptions, we agreed to make pro rata payments to each purchaser as liquidated damages in an amount equal to 1.0% of the aggregate amount paid by the purchaser for the registrable securities then held by the purchaser, per 30-day period or pro rata for any portion thereof for each such 30-day period during which such event continues, subject to certain caps set forth in the Astellas Registration Rights Agreement.

If we propose to register shares of our common stock for our own account or for the account of other stockholders, the holders of Astellas Shares are entitled to notice of the registration and are entitled to include their shares of common stock in the registration statement. These piggyback registration rights are subject to specified conditions and limitations, including the right of the underwriters to limit the number of shares included in any such registration under specified circumstances.

SSI Registration Rights

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. Under the terms of the SSI Securities Purchase Agreement, we agreed to file a registration statement covering the resale of 705,218 shares of our common stock issued and sold to the SSI Investors, or the SSI Shares, and 525,000 shares of common stock issuable upon the exercise of outstanding warrants to purchase shares of our common stock, or

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SSI Warrant Shares, issued and sold to the SSI Investors in a private placement. We agreed to use reasonable best efforts to keep such registration statement continuously effective until the earlier of (i) the date the SSI Shares and SSI 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.

In the event sales cannot be made pursuant to the registration statement, subject to certain limited exceptions, we agreed to make pro rata payments to each purchaser as liquidated damages in an amount equal to 1.0% of the aggregate amount paid by the purchaser for the registrable securities then held by the purchaser, per 30-day period or pro rata for any portion thereof for each such 30-day period during which such event continues, subject to certain caps set forth in the SSI Securities Purchase Agreement.

If we propose to register shares of our common stock for our own account or for the account of other stockholders, the holders of SSI Shares and SSI Warrant Shares are entitled to notice of the registration and are entitled to include their shares of common stock in the registration statement. These piggyback registration rights are subject to specified conditions and limitations, including the right of the underwriters to limit the number of shares included in any such registration under specified circumstances.

2023 Private Placement Registration Rights

In August 2023, we entered into a securities purchase agreement, or the 2023 Purchase Agreement, with certain institutional and other accredited investors, or the PIPE Investors. Under the terms of the 2023 Purchase Agreement, we agreed to prepare and file one or more registration statements to register for resale 122,412,376 shares of our common stock issued and sold to the PIPE Investors and 44,250,978 shares of our common stock issuable upon the exercise of outstanding pre-funded warrants to purchase shares of our common stock issued and sold to the PIPE Investors, collectively the PIPE Shares. 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 PIPE Shares (assuming cashless exercise of the pre-funded warrants) held by or issuable to a Holder (as defined in the 2023 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 is suspended, ceases to remain continuously effective or is unavailable for purchasers to sell registrable securities, subject to certain limited exceptions, we 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 2023 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 2023 Purchase Agreement.

Board Observer Rights

In October 2022, we entered into a securities purchase agreement with Astellas, or the Astellas SPA, pursuant to which Astellas has the right to designate one individual to attend all meetings of the board of directors in a non-voting observer capacity, or the Astellas Board Observer. The Astellas Board Observer is entitled to all notices, minutes, consents and other materials provided to our directors at the same time and in the same manner as provided to such directors. The Astellas Board Observer right terminates upon a Change of Control (as defined in the Astellas SPA) or when Astellas no longer holds shares of our common stock.

In June 2023, our board of directors appointed Paul B. Manning as a non-voting board observer, and in such capacity, Mr. Manning may attend, in a non-voting capacity, all meetings of the Board.

Anti-Takeover Provisions

Section 203 of the DGCL

We are subject to Section 203 of the DGCL, or Section 203, which prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, with the following exceptions:

- before such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction began, excluding for purposes of determining the voting stock outstanding, but not the outstanding voting stock owned by the interested stockholder, those shares owned (i) by persons who are directors and also officers and (ii) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- on or after such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock that is not owned by the interested stockholder.

In general, Section 203 defines a “business combination” to include the following:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;
- subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits by or through the corporation.

In general, Section 203 defines an “interested stockholder” as an entity or person who, together with the person’s affiliates and associates, beneficially owns, or within three years prior to the time of determination of interested stockholder status did own, 15% or more of the outstanding voting stock of the corporation.

Certificate of Incorporation and Bylaws

Our certificate of incorporation provides for our board of directors to be divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. Because our stockholders do not have cumulative voting rights, stockholders holding a majority of the shares of common stock outstanding will be able to elect all of our directors. Our certificate of incorporation and bylaws provide that directors may be removed by the stockholders only for cause upon the vote of 66 2/3% or more of our outstanding common stock. Furthermore, the authorized number of directors may be changed only by resolution of the board of directors, and vacancies and newly created directorships on the board of directors may, except as otherwise required by law or determined by the board, only be filled by a majority vote of the directors then serving on the board, even though less than a quorum.

Our certificate of incorporation and bylaws also provide that all stockholder actions must be effected at a duly called meeting of stockholders and will eliminate the right of stockholders to act by written consent without a

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meeting. The bylaws provide that only the Chairman of the board, Chief Executive Officer or the board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors may call a special meeting of stockholders. The bylaws also provide that stockholders seeking to present proposals before a meeting of stockholders to nominate candidates for election as directors at a meeting of stockholders must provide timely advance notice in writing, and will specify requirements as to the form and content of a stockholder's notice.

Our certificate of incorporation and bylaws provide that the stockholders cannot amend many of the provisions described above except by a vote of 66 2/3% or more of our outstanding common stock.

Our certificate of incorporation gives our board of directors the authority, without further action by our stockholders, to issue up to 10,000,000 shares of preferred stock in one or more series, with any rights, preferences and privileges as they may designate, including the right to approve an acquisition or other change in control.

The combination of these provisions will make it more difficult for our existing stockholders to replace our board of directors as well as for another party to obtain control of us by replacing our board of directors. Since our board of directors has the power to retain and discharge our officers, these provisions could also make it more difficult for existing stockholders or another party to effect a change in management. In addition, the authorization of undesignated preferred stock makes it possible for our board of directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to change control of our company.

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to reduce our vulnerability to hostile takeovers and to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and may have the effect of delaying changes in control or management of our company. As a consequence, these provisions may also inhibit fluctuations in the market price of our stock that could result from actual or rumored takeover attempts. We believe that the benefits of these provisions, including increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure our company, outweigh the disadvantages of discouraging takeover proposals, because negotiation of takeover proposals could result in an improvement of their terms.

Choice of Forum

Our certificate of incorporation provides that the Court of Chancery of the state of Delaware will be the exclusive forum for the following types of actions or proceedings under Delaware statutory or common law:

- any derivative action or proceeding brought on our behalf;
- any action asserting a breach of fiduciary duty;
- any action asserting a claim against us arising pursuant to the DGCL, our certificate of incorporation or our bylaws;
- any claim or cause of action seeking to interpret, apply, enforce or determine the validity of our certificate of incorporation or our amended and restated bylaws;
- any claim or cause of action as to which the DGCL confers jurisdiction on the Court of Chancery of the state of Delaware; or
- any action asserting a claim against us that is governed by the internal affairs doctrine.

The provision does not apply to suits brought to enforce a duty or liability created by the Exchange Act or to claims for which the federal courts have exclusive jurisdiction. Furthermore, Section 22 of the Securities Act

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creates concurrent jurisdiction for federal and state courts over all such Securities Act actions. Accordingly, both state and federal courts have jurisdiction to entertain such claims. To prevent having to litigate claims in multiple jurisdictions and the threat of inconsistent or contrary rulings by different courts, among other considerations, our certificate of incorporation also provides that unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States shall be the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. Although our certificate of incorporation contains the choice of forum provision described above, it is possible that a court could rule that such a provision is inapplicable for a particular claim or action or that such provision is unenforceable.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Equiniti Trust Company, LLC (f/k/a American Stock Transfer & Trust Company, LLC), with offices at 55 Challenger Road, Ridgefield Park, NJ 07660. The transfer agent for any series of preferred stock that we may offer under this prospectus will be named and described in the prospectus supplement for that series.

Listing on Nasdaq

Our common stock is listed on The Nasdaq Global Select Market under the symbol “TSHA.”

DESCRIPTION OF THE PRE-FUNDED WARRANTS

The following is a brief summary of certain terms and conditions of the pre-funded warrants being offered by us. The following description is subject in all respects to the provisions contained in the pre-funded warrants.

Form

The pre-funded warrants will be issued as individual warrant agreements to each individual purchaser of a pre-funded warrant. The form of pre-funded warrant will be filed as an exhibit to a Current Report on Form 8-K that we will file with the SEC.

Term

The pre-funded warrants do not expire.

Exercisability

The pre-funded warrants are exercisable at any time after their original issuance. The pre-funded warrants will be exercisable, at the option of each holder, in whole or in part, by delivering to us a duly executed exercise notice and by payment in full of the exercise price in immediately available funds for the number of shares of our common stock purchased upon such exercise. As an alternative to payment of the exercise price in immediately available funds, the holder may elect to exercise the pre-funded warrant through a cashless exercise, in which case the holder would receive upon such exercise the net number of shares of our common stock determined according to the formula set forth in the pre-funded warrant. No fractional shares of our common stock will be issued in connection with the exercise of a pre-funded warrant. In lieu of fractional shares, we will, at our election, either pay the holder an amount in cash equal to such fraction multiplied by the exercise price or round up to the next whole share.

Exercise Limitations

Under the pre-funded warrants, we may not effect the exercise of any pre-funded warrant, and a holder will not be entitled to exercise any portion of any pre-funded warrant, which, upon giving effect to such exercise, would cause (i) the aggregate number of shares of our common stock beneficially owned by the holder (together with its affiliates) to exceed 4.99% or 9.99%, as the case may be, of the number of shares of our common stock outstanding immediately prior to or after giving effect to the exercise, or (ii) the combined voting power of our securities beneficially owned by the holder (together with its affiliates) to exceed 4.99% or 9.99%, as the case may be, of the combined voting power of all of our securities then outstanding immediately prior to or after giving effect to the exercise, as such percentage ownership is determined in accordance with the terms of the pre-funded warrants, subject to such holder's rights under the pre-funded warrant to increase or decrease such percentage to another percentage not in excess of 19.99% upon at least 61 days' prior notice from such holder to us.

Exercise Price

The exercise price per whole share of our common stock issuable upon the exercise of the pre-funded warrants is \$0.001 per share of our common stock. The exercise price of the pre-funded warrants and the number of shares of our common stock issuable upon exercise of the pre-funded warrants are subject to appropriate adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting our common stock and also upon any distributions of assets, including cash, stock or other property to our stockholders.

Transferability

Subject to applicable laws, the pre-funded warrants may be offered for sale, sold, transferred or assigned without our consent. The pre-funded warrants will be held in definitive form by the purchasers. The ownership of the pre-funded warrants and any transfers of the pre-funded warrants will be registered in a warrant register maintained by us or our transfer agent.

Exchange Listing

We do not plan on applying to list the pre-funded warrants on The Nasdaq Global Select Market, any other national securities exchange or any other nationally recognized trading system.

Subsequent Rights Offerings

If at any time we grant, issue or sell any specified common stock equivalents or rights to purchase stock, warrants, securities or other property to the record holders of any class of shares of common stock, or the Purchase Rights, then the holder of a pre-funded warrant will be entitled to acquire, upon the terms applicable to such Purchase Rights, the aggregate Purchase Rights which the holder could have acquired if the holder had held the number of shares of common stock acquirable upon complete exercise of the holder's pre-funded warrant, without regard to any limitations on exercise, including without limitation, such holder's beneficial ownership limitation, immediately before the date on which a record is taken for the grant, issuance or sale of such Purchase Rights, or, if no such record is taken, the date as of which the record holders of shares of common stock are to be determined for the grant, issue or sale of such Purchase Rights (provided, however, that, to the extent that the holder's right to participate in any such Purchase Right would result in the holder exceeding the holder's beneficial ownership limitation, then the holder shall not be entitled to participate in such Purchase Right to such extent (or beneficial ownership of such shares of common stock as a result of such Purchase Right to such extent) and such Purchase Right to such extent shall be held in abeyance for the holder until such time, if ever, as its right thereto would not result in the holder exceeding the holder's beneficial ownership limitation).

Pro Rata Distributions

During such time as a holder's pre-funded warrant is outstanding, if we declare or make any dividend or other distribution of our assets (or rights to acquire its assets) to holders of shares of our common stock, by way of return of capital or otherwise (including, without limitation, any distribution of cash, stock or other securities, property or options by way of a dividend, spin off, reclassification, corporate rearrangement, scheme of arrangement or other similar transaction), or a Distribution, at any time after the issuance of the pre-funded warrants, then, in each such case, the holder of a pre-funded warrant shall be entitled to participate in such Distribution to the same extent that the holder would have participated therein if the holder had held the number of shares of common stock acquirable upon complete exercise of the pre-funded warrant (without regard to any limitations on exercise, including without limitation, the holder's beneficial ownership limitation) immediately before the date of which a record is taken for such Distribution, or, if no such record is taken, the date as of which the record holders of shares of common stock are to be determined for the participation in such Distribution (provided, however, that, to the extent that the holder's right to participate in any such Distribution would result in the holder exceeding the holder's beneficial ownership limitation, then the holder shall not be entitled to participate in such Distribution to such extent (or in the beneficial ownership of any shares of common stock as a result of such Distribution to such extent) and the portion of such Distribution shall be held in abeyance for the benefit of the holder until such time, if ever, as its right thereto would not result in such holder exceeding its beneficial ownership limitation).

Fundamental Transactions

In the event of a fundamental transaction, as described in the pre-funded warrants and generally including any reorganization, recapitalization or reclassification of our common stock, the sale, transfer or other disposition of

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all or substantially all of our properties or assets, our consolidation or merger with or into another person, the acquisition of more than 50% of our outstanding common stock, or any person or group becoming the beneficial owner of 50% of the voting power represented by our outstanding common stock, upon consummation of such a fundamental transaction, the holders of the pre-funded warrants will be entitled to receive upon exercise of the pre-funded warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the pre-funded warrants immediately prior to such fundamental transaction without regard to any limitations on exercise contained in the pre-funded warrants, and any additional consideration receivable as a result of such fundamental transaction.

No Rights as a Stockholder

Except by virtue of such holder's ownership of shares of our common stock, the holder of a pre-funded warrant does not have the rights or privileges of a holder of our common stock, including any voting rights, until the holder exercises the pre-funded warrant.

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES

The following is a general discussion of the material U.S. federal income tax considerations of the purchase, ownership and disposition of shares of our common stock issued pursuant to this offering, or the shares, and the purchase, ownership and disposition of pre-funded warrants. The shares and the pre-funded warrants are collectively referred to herein as our “securities.” All prospective holders of our securities should consult their tax advisors with respect to the U.S. federal, state, local and non-U.S. tax consequences of the purchase, ownership and disposition of our securities.

This discussion is not a complete analysis of all potential U.S. federal income tax consequences relating to the purchase, ownership and disposition of our securities. This discussion is based on current provisions of the U.S. Internal Revenue Code of 1986, as amended, which we refer to as the Code, existing U.S. Treasury Regulations promulgated thereunder, published administrative pronouncements and rulings of the U.S. Internal Revenue Service, or the IRS, and judicial decisions, all as in effect as of the date of this prospectus supplement. These authorities are subject to change and to differing interpretation, possibly with retroactive effect. Any change or differing interpretation could alter the tax consequences to holders described in this discussion. There can be no assurance that a court or the IRS will not challenge one or more of the tax consequences described herein, and we have not obtained, nor do we intend to obtain, a ruling with respect to the U.S. federal income tax consequences to a holder of the purchase, ownership or disposition of our securities.

We assume in this discussion that a holder holds our securities as a “capital asset” within the meaning of Section 1221 of the Code (generally, property held for investment). This discussion does not address all aspects of U.S. federal income taxation that may be relevant to a particular holder in light of that holder’s individual circumstances, nor does it address any alternative minimum, Medicare contribution, estate or gift tax consequences, or any aspects of U.S. state, local or non-U.S. taxes or any other U.S. federal tax laws, nor does this discussion address the special accounting rules in Section 451(b) of the Code. This discussion also does not address consequences relevant to holders subject to special tax rules, such as holders that own, or are deemed to own, more than 5% of our capital stock (except to the extent specifically set forth below), corporations that accumulate earnings to avoid U.S. federal income tax, tax-exempt organizations, governmental organizations, banks, financial institutions, investment funds, insurance companies, brokers, dealers or traders in securities, commodities or currencies, regulated investment companies or real estate investment trusts, persons that have a “functional currency” other than the U.S. dollar, tax-qualified retirement plans, holders who hold or receive our securities pursuant to the exercise of employee stock options or otherwise as compensation, holders holding our securities as part of a hedge, straddle or other risk reduction strategy, conversion transaction or other integrated investment, holders deemed to sell our securities under the constructive sale provisions of the Code, controlled foreign corporations, passive foreign investment companies and certain former U.S. citizens or long-term residents.

In addition, this discussion does not address the tax treatment of partnerships (or entities or arrangements that are treated as partnerships or disregarded entities for U.S. federal income tax purposes) or persons that hold our securities through such partnerships. If a partnership, including any entity or arrangement treated as a partnership for U.S. federal income tax purposes, holds our securities, the U.S. federal income tax treatment of a partner in such partnership generally will depend upon the status of the partner, and the activities of the partnership and certain determinations made at the partner level. Such partners and partnerships should consult their tax advisors regarding the tax consequences of the purchase, ownership and disposition of our securities.

Treatment of Pre-Funded Warrants

Although it is not entirely free from doubt, we believe a pre-funded warrant should be treated as a share for U.S. federal income tax purposes and a holder of pre-funded warrants should generally be taxed in the same manner as a holder of shares, as described below. Accordingly, no gain or loss should be recognized (other than with respect to cash paid in lieu of a fractional share) upon the exercise of a pre-funded warrant and, upon exercise, the

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holding period of a pre-funded warrant should carry over to the share received. Similarly, the tax basis of the pre-funded warrant should carry over to the shares received upon exercise, increased by the exercise price of \$0.001 per share. However, our characterization is not binding on the IRS, and the IRS may treat the pre-funded warrants as warrants to acquire our shares. If so, the amount and character of your gain or loss with respect to an investment in our pre-funded warrants could change. Accordingly, each holder should consult his, her or its own tax advisor regarding the risks associated with the acquisition of pre-funded warrants pursuant to this offering (including potential alternative characterizations). Except where specifically noted below, the balance of this discussion generally assumes that the characterization described above is respected for U.S. federal income tax purposes. However, some portions of the below discussion make reference to potential consequences associated with the acquisition, ownership and disposition of the pre-funded warrants independent of their potential characterization as shares for U.S. federal income tax purposes.

Tax Considerations Applicable to U.S. Holders

Definition of U.S. Holder

In general, a “U.S. holder” means a beneficial owner of our securities (other than a partnership or an entity or arrangement treated as a partnership for U.S. federal income tax purposes) that is, for U.S. federal income tax purposes:

- an individual who is a citizen or resident of the United States;
- a corporation, or an entity treated as a corporation for U.S. federal income tax purposes, created or organized in the United States or under the laws of the United States or of any state thereof or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust if (a) a U.S. court can exercise primary supervision over the trust’s administration and one or more U.S. persons have the authority to control all of the trust’s substantial decisions or (b) the trust has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a U.S. person.

Distributions on the Shares and Pre-Funded Warrants

We do not anticipate declaring or paying any future distributions. However, if we do make distributions on our securities, such distributions will constitute dividends to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles, and will be includible in your income as ordinary income when received. However, with respect to dividends received by individuals, such dividends are generally taxed at the lower applicable long-term capital gains rates, provided certain holding period and other requirements are satisfied. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the U.S. holder’s investment, up to such U.S. holder’s adjusted tax basis in our securities. Any remaining excess will be treated as capital gain from the sale or exchange of such securities, subject to the tax treatment described below in “—Sale or Other Taxable Disposition of the Shares or Pre-Funded Warrants.”

Sale or Other Taxable Disposition of the Shares or Pre-Funded Warrants

Upon the sale, exchange or other taxable disposition of our securities, a U.S. holder generally will recognize capital gain or loss equal to the difference between the amount of cash and the fair market value of any property received upon the sale, exchange or other taxable disposition and such U.S. holder’s adjusted tax basis in our securities. This capital gain or loss will be long-term capital gain or loss if the U.S. holder’s holding period in such securities is more than one year at the time of the sale, exchange or other taxable disposition. Long-term capital gains recognized by certain non-corporate U.S. holders, including individuals, generally will be subject to reduced rates of U.S. federal income tax. The deductibility of capital losses is subject to certain limitations.

Constructive Distributions on Pre-Funded Warrants

A U.S. holder of a pre-funded warrant may, in some circumstances, be deemed to have received a distribution subject to U.S. federal income tax as a result of an adjustment or the non-occurrence of an adjustment to the exercise price or number of shares of common stock issuable upon exercise of the pre-funded warrant. U.S. holders should consult their tax advisors regarding the proper treatment of any adjustments (or the non-occurrence of any adjustments) to the pre-funded warrants.

Backup Withholding and Information Reporting

A U.S. holder may be subject to information reporting and backup withholding when such holder receives payments on our securities (including constructive distributions) or receives proceeds from the sale or other taxable disposition of our securities. Certain U.S. holders are exempt from backup withholding, including C corporations and certain tax-exempt organizations. A U.S. holder will be subject to backup withholding if such holder is not otherwise exempt and such holder:

- fails to furnish the holder's taxpayer identification number, which for an individual is ordinarily his or her social security number;
- furnishes an incorrect taxpayer identification number;
- is notified by the IRS that the holder previously failed to properly report payments of interest or dividends; or
- fails to certify under penalties of perjury that the holder has furnished a correct taxpayer identification number and that the IRS has not notified the holder that the holder is subject to backup withholding.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a U.S. holder's U.S. federal income tax liability, provided the required information is timely furnished to the IRS. U.S. holders should consult their tax advisors regarding their qualification for an exemption from backup withholding and the procedures for obtaining such an exemption.

Tax Considerations Applicable to Non-U.S. Holders

Definition of non-U.S. Holder

For purposes of this discussion, a "non-U.S. holder" is a beneficial owner of our securities that is neither a U.S. holder nor a partnership or an entity or arrangement treated as a partnership for U.S. federal income tax purposes.

Distributions on the Shares and Pre-Funded Warrants

If we make distributions on our securities such distributions will constitute dividends to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder's investment, up to such non-U.S. holder's adjusted tax basis in our securities. Any remaining excess will be treated as capital gain from the sale or exchange of such securities, subject to the tax treatment described below in "—Gain on Sale, Exchange or Other Taxable Disposition of Our Shares or Pre-Funded Warrants."

Dividends paid to a non-U.S. holder will generally be subject to withholding of U.S. federal income tax at a 30% rate of the gross amount of the dividend or such lower rate as may be specified by an applicable income tax treaty between the United States and such non-U.S. holder's country of residence for purposes of such treaty.

Dividends that are treated as effectively connected with a trade or business conducted by a non-U.S. holder within the United States and, if an applicable income tax treaty so provides, that are attributable to a permanent

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establishment or a fixed base maintained by the non-U.S. holder within the United States, are generally exempt from the 30% withholding tax if the non-U.S. holder satisfies applicable certification and disclosure requirements. However, such U.S. effectively connected income, net of specified deductions and credits, is taxed at the same U.S. federal income tax rates applicable to U.S. persons (as defined in the Code). Any U.S. effectively connected income received by a non-U.S. holder that is a corporation may also, under certain circumstances, be subject to an additional “branch profits tax” at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such non-U.S. holder’s country of residence for purposes of such treaty.

To claim a reduction or exemption from withholding, a non-U.S. holder generally will be required to provide (a) a properly executed IRS Form W-8BEN or IRS Form W-8BEN-E (or successor form) and satisfy applicable certification and other requirements to claim the benefit of an applicable income tax treaty between the United States and such non-U.S. holder’s country of residence, or (b) a properly executed IRS Form W-8ECI stating that dividends are not subject to withholding because they are effectively connected with such non-U.S. holder’s conduct of a trade or business within the United States. Non-U.S. holders are urged to consult their tax advisors regarding their entitlement to benefits under a relevant income tax treaty.

A non-U.S. holder that is eligible for a reduced rate of U.S. withholding tax under an income tax treaty may obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS.

Distributions will also be subject to the discussion below under the headings “—Backup Withholding and Information Reporting” and “—Foreign Accounts.”

Gain on Sale, Exchange or Other Taxable Disposition of Our Shares or Pre-Funded Warrants

Subject to the discussion below under the headings “—Backup Withholding and Information Reporting” and “—Foreign Accounts,” in general, a non-U.S. holder will not be subject to any U.S. federal income tax on any gain realized upon such non-U.S. holder’s sale, exchange or other taxable disposition of our securities unless:

- the gain is effectively connected with a U.S. trade or business of the non-U.S. holder and, if an applicable income tax treaty so provides, is attributable to a permanent establishment or a fixed base maintained in the United States by such non-U.S. holder, in which case the non-U.S. holder generally will be taxed at the U.S. federal income tax rates applicable to U.S. persons (as defined in the Code) and, if the non-U.S. holder is a foreign corporation, the branch profits tax described above in “—Distributions on the Shares and Pre-Funded Warrants” also may apply;
- the non-U.S. holder is a nonresident alien individual who is present in the United States for 183 days or more in the taxable year of the disposition and certain other conditions are met, in which case the non-U.S. holder will be subject to a 30% U.S. federal income tax (or such lower rate as may be specified by an applicable income tax treaty) on the net gain derived from the disposition, which may be offset by U.S. source capital losses of the non-U.S. holder, if any (even though the individual is not considered a resident of the United States); or
- we are, or have been, at any time during the five-year period preceding such disposition (or the non-U.S. holder’s holding period, if shorter) a “U.S. real property holding corporation” in which case such non-U.S. holder generally will be taxed on its net gain derived from the disposition as effectively connected income taxable at the U.S. federal income tax rates applicable to U.S. persons (as defined in the Code); however, the branch profits tax described above will not apply to a U.S. holder that is a foreign corporation. Generally, a corporation is a U.S. real property holding corporation if the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. Although there can be no assurance, we do not believe that we are, or have been, a U.S. real

property holding corporation, or that we are likely to become one in the future. Even if we are or become a U.S. real property holding corporation, provided that our common stock is regularly traded, as defined by applicable U.S. Treasury Regulations, on an established securities market, our securities will be treated as a U.S. real property interest only with respect to a non-U.S. holder that holds more than 5% of our securities (as determined under U.S. federal income tax principles), directly or indirectly, actually or constructively, during the shorter of the 5-year period ending on the date of the disposition or the period that the non-U.S. holder held our securities. There can be no assurance that our common stock will continue to qualify as regularly traded on an established securities market.

Constructive Distributions on Pre-Funded Warrants

A non-U.S. holder of pre-funded warrants can be treated as receiving deemed payment of a taxable dividend under certain circumstances as a result of an adjustment or the non-occurrence of an adjustment to the exercise price or number of shares issuable upon exercise of the pre-funded warrant. Any resulting withholding tax attributable to deemed dividends may be collected from other amounts payable or distributable to the non-U.S. holder. Non-U.S. holders should consult their tax advisors regarding the proper treatment of any adjustments (or the non-occurrence of any adjustments) to the pre-funded warrants.

Backup Withholding and Information Reporting

We must report annually to the IRS and to each non-U.S. holder the gross amount of the distributions (including constructive distributions) on our securities paid to such non-U.S. holder and the tax withheld, if any, with respect to such distributions. Non-U.S. holders will have to comply with specific certification procedures to establish that the holder is not a U.S. person (as defined in the Code) in order to avoid backup withholding at the applicable rate with respect to any dividends on our securities. A non-U.S. holder generally will not be subject to U.S. backup withholding with respect to payments of distributions on our securities if it certifies its non-U.S. status by providing a valid IRS Form W-8BEN or IRS Form W-8BEN-E (or successor form) or IRS Form W-8ECI, or otherwise establishes an exemption; provided we do not have actual knowledge or reason to know such non-U.S. holder is a U.S. person, as defined in the Code. Distributions paid to non-U.S. holders subject to the U.S. withholding tax, as described above in “—Distributions on the Shares and Pre-Funded Warrants” generally will be exempt from U.S. backup withholding.

Information reporting and backup withholding generally will apply to the proceeds of a disposition of our securities by a non-U.S. holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a non-U.S. holder and satisfies certain other requirements, or otherwise establishes an exemption.

Copies of information returns may be made available to the tax authorities of the country in which the non-U.S. holder resides or is established under the provisions of a specific treaty or agreement.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder may be allowed as a credit against the non-U.S. holder's U.S. federal income tax liability, if any, and may entitle such holder to a refund, provided that the required information is timely furnished to the IRS.

Foreign Accounts

The Code generally imposes a U.S. federal withholding tax of 30% on dividends and, subject to the discussion below regarding proposed regulations issued by the U.S. Treasury Department, the gross proceeds of a disposition of our securities paid to a “foreign financial institution” (as defined in the Code), unless such institution enters into an agreement with the U.S. government to, among other things, withhold on certain payments and to collect and provide to the U.S. tax authorities substantial information regarding accounts held by

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certain “specific United States persons” or “United States owned foreign entities” (each as defined in the Code), or otherwise qualifies for an exemption from these rules. A U.S. federal withholding tax of 30% also applies to dividends and, subject to the discussion below regarding proposed regulations issued by the U.S. Treasury Department, will apply to the gross proceeds of a disposition of our securities paid to a “non-financial foreign entity” (as defined in the Code), unless such entity provides the withholding agent with either a certification that it does not have any “substantial United States owners” (as defined in the Code), provides information regarding each substantial United States owners of the entity, or otherwise qualifies for an exemption from these rules. Under certain circumstances, a non-U.S. holder might be eligible for refunds or credits of such taxes. An intergovernmental agreement between the United States and an applicable foreign country may modify the requirements described in this paragraph.

The withholding provisions described above currently apply to dividends paid on our securities. The U.S. Treasury Department released proposed regulations which, if finalized in their present form, would eliminate the U.S. federal withholding tax of 30% applicable to the gross proceeds of a sale or other disposition of our securities. In its preamble to such proposed regulations, the U.S. Treasury Department stated that taxpayers may generally rely on the proposed regulations until final regulations are issued.

EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS TAX ADVISOR REGARDING THE PARTICULAR U.S. FEDERAL, STATE AND LOCAL AND NON-U.S. TAX CONSEQUENCES OF PURCHASING, HOLDING AND DISPOSING OF OUR SECURITIES, INCLUDING THE CONSEQUENCES OF ANY PROPOSED CHANGE IN APPLICABLE LAWS.

UNDERWRITING

Subject to the terms and conditions set forth in the underwriting agreement, dated May 28, 2025, among us and Jefferies LLC, BofA Securities, Inc., Piper Sandler & Co. and Barclays Capital Inc. as the representatives of the underwriters named below and the joint book-running managers of this offering, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the respective number of shares of common stock and pre-funded warrants shown opposite its name below:

<u>Underwriter</u>	<u>Number of Shares</u>	<u>Number of Pre-Funded Warrants</u>
Jefferies LLC	16,696,970	9,212,121
BofA Securities, Inc.	12,010,101	6,626,263
Piper Sandler & Co.	12,010,101	6,626,263
Barclays Capital Inc.	6,151,515	3,393,939
Total	<u>46,868,687</u>	<u>25,858,586</u>

The underwriting agreement provides that the obligations of the several underwriters are subject to certain conditions precedent such as the receipt by the underwriters of officers' certificates and legal opinions and approval of certain legal matters by their counsel. The underwriting agreement provides that the underwriters will purchase all of the shares of common stock and pre-funded warrants if any of them are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the non-defaulting underwriters may be increased or the underwriting agreement may be terminated. We have agreed to indemnify the underwriters and certain of their controlling persons against certain liabilities, including liabilities under the Securities Act, and to contribute to payments that the underwriters may be required to make in respect of those liabilities.

The underwriters have advised us that, following the completion of this offering, they currently intend to make a market in the common stock as permitted by applicable laws and regulations. However, the underwriters are not obligated to do so, and the underwriters may discontinue any market-making activities at any time without notice in their sole discretion. Accordingly, no assurance can be given as to the liquidity of the trading market for the shares of common stock and pre-funded warrants, that you will be able to sell any of the shares of common stock and pre-funded warrants held by you at a particular time or that the prices that you receive when you sell will be favorable.

The underwriters are offering the shares of common stock and pre-funded warrants subject to their acceptance of the shares of common stock and pre-funded warrants from us and subject to prior sale. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commission and Expenses

The underwriters have advised us that they propose to offer the shares of common stock and pre-funded warrants to the public at the public offering price set forth on the cover page of this prospectus supplement and to certain dealers, which may include the underwriters, at that price less a concession not in excess of \$0.099 per share of common stock or pre-funded warrant. After the offering, the public offering price and concession to dealers may be reduced by the representatives. No such reduction will change the amount of proceeds to be received by us as set forth on the cover page of this prospectus supplement.

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The following table shows the public offering price, the underwriting discounts and commissions that we are to pay the underwriters and the proceeds, before expenses, to us in connection with this offering. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares of common stock.

			Total	
	Per Share of Common Stock	Per Pre-Funded Warrant	Without Option to Purchase Additional Shares	With Option to Purchase Additional Shares
Public offering price	\$ 2.75	\$ 2.749	\$ 199,974,142	\$ 229,974,140
Underwriting discounts and commissions paid by us	\$ 0.165	\$ 0.165	\$ 12,000,000	\$ 13,800,000
Proceeds to us, before expenses	\$ 2.585	\$ 2.584	\$ 187,974,142	\$ 216,174,140

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately \$525,000. In addition, the underwriters have agreed to reimburse us for certain expenses incurred by us in connection with this offering upon closing of this offering.

Listing

Our common stock is listed on the Nasdaq Global Select Market under the trading symbol "TSHA".

There is no established public trading market for the pre-funded warrants, and we do not expect a market to develop. We do not intend to list the pre-funded warrants on any national securities exchange or nationally recognized trading system.

Option to Purchase Additional Shares

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase, from time to time, in whole or in part, up to an aggregate of 10,909,090 shares of common stock from us at the public offering price set forth on the cover page of this prospectus supplement, less underwriting discounts and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to specified conditions, to purchase a number of additional shares of common stock proportionate to that underwriter's initial purchase commitment as indicated in the table above.

No Sales of Similar Securities

We, our executive officers and our directors have agreed with the underwriters, subject to certain exceptions, not to dispose of or hedge any of their common stock or securities convertible into or exchangeable for shares of common stock during the period from the date of this prospectus supplement continuing through the date 60 days after the date of this prospectus supplement, except with the prior written consent of the representatives and subject to certain exceptions.

Stabilization

The underwriters have advised us that they may engage in short sale transactions, stabilizing transactions, syndicate covering transactions or the imposition of penalty bids in connection with this offering. These activities may have the effect of stabilizing or maintaining the market price of the shares of common stock at a level above that which might otherwise prevail in the open market. Establishing short sales positions may involve either "covered" short sales or "naked" short sales.

"Covered" short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares of our common stock in this offering. The underwriters may close out any covered short

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position by either exercising their option to purchase additional shares of our common stock or purchasing shares of our common stock in the open market. In determining the source of shares of common stock to close out the covered short position, the underwriters will consider, among other things, the price of shares of common stock available for purchase in the open market as compared to the price at which they may purchase shares of common stock through the option to purchase additional shares of common stock.

“Naked” short sales are sales in excess of the option to purchase additional shares of our common stock. The underwriters must close out any naked short position by purchasing shares of common stock in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the shares of our common stock in the open market after pricing that could adversely affect investors who purchase in this offering.

A stabilizing bid is a bid for the purchase of shares of common stock on behalf of the underwriters for the purpose of fixing or maintaining the price of the shares of common stock. A syndicate covering transaction is the bid for or the purchase of shares of common stock on behalf of the underwriters to reduce a short position incurred by the underwriters in connection with the offering. Similar to other purchase transactions, the underwriter’s purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. A penalty bid is an arrangement permitting the underwriters to reclaim the selling concession otherwise accruing to a syndicate member in connection with the offering if the common stock originally sold by such syndicate member are purchased in a syndicate covering transaction and therefore have not been effectively placed by such syndicate member.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. The underwriters are not obligated to engage in these activities and, if commenced, any of the activities may be discontinued at any time.

The underwriters may also engage in passive market making transactions in our shares of common stock on the Nasdaq Global Select Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers or sales of shares of our common stock in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker’s bid, that bid must then be lowered when specified purchase limits are exceeded.

Electronic Distribution

A prospectus in electronic format may be made available by e-mail or through online services maintained by one or more of the underwriters or their affiliates. In those cases, prospective investors may view offering terms online and may be allowed to place orders online. The underwriters may agree with us to allocate a specific number of shares of common stock and pre-funded warrants for sale to online brokerage account holders. Any such allocation for online distributions will be made by the underwriters on the same basis as other allocations. Other than the prospectus in electronic format, the information on the underwriters’ web sites and any information contained in any other web site maintained by any of the underwriters is not part of this prospectus supplement, has not been approved and/or endorsed by us or the underwriters and should not be relied upon by investors.

Other Activities and Relationships

The underwriters and certain of their affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment

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management, investment research, principal investment, hedging, financing and brokerage activities. The underwriters and certain of their affiliates have, from time to time, performed, and may in the future perform, various commercial and investment banking and financial advisory services for us and our affiliates, for which they received or will receive customary fees and expenses.

In the ordinary course of their various business activities, the underwriters and certain of their affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers, and such investment and securities activities may involve securities and/or instruments issued by us and our affiliates. If the underwriters or their respective affiliates have a lending relationship with us, they routinely hedge their credit exposure to us consistent with their customary risk management policies. The underwriters and their respective affiliates may hedge such exposure by entering into transactions which consist of either the purchase of credit default swaps or the creation of short positions in our securities or the securities of our affiliates, including potentially the shares of common stock offered hereby. Any such short positions could adversely affect future trading prices of the shares of common stock offered hereby. The underwriters and certain of their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Disclaimers About Non-U.S. Jurisdictions

European Economic Area

In relation to each Member State of the European Economic Area (each a “Relevant State”), no shares of common stock or pre-funded warrants have been offered or will be offered pursuant to the offering to the public in that Relevant State prior to the publication of a prospectus in relation to the shares of common stock or pre-funded warrants which has been approved by the competent authority in that Relevant State or, where appropriate, approved in another Relevant State and notified to the competent authority in that Relevant State, all in accordance with the Prospectus Regulation, except that offers of shares of common stock or pre-funded warrants may be made to the public in that Relevant State at any time under the following exemptions under the Prospectus Regulation:

- a) to any legal entity which is a qualified investor as defined under Article 2 of the Prospectus Regulation;
- b) to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the Prospectus Regulation), subject to obtaining the prior consent of the representatives for any such offer; or
- c) in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of shares of common stock or pre-funded warrants shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation and each person who initially acquires any shares of common stock or pre-funded warrants or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with each of the underwriters and us that it is a “qualified investor” within the meaning of Article 2(e) of the Prospectus Regulation.

In the case of any shares of common stock or pre-funded warrants being offered to a financial intermediary as that term is used in the Prospectus Regulation, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares or pre-funded warrants acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any shares of common stock or pre-funded warrants to the public other than their offer or resale in a Relevant State to qualified investors as so defined or in

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circumstances in which the prior consent of the underwriters has been obtained to each such proposed offer or resale.

For the purposes of this provision, the expression an “offer to the public” in relation to the shares of common stock in any Relevant State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares of common stock or pre-funded warrants to be offered so as to enable an investor to decide to purchase or subscribe for any shares of common stock or pre-funded warrants, and the expression “Prospectus Regulation” means Regulation (EU) 2017/1129.

United Kingdom

No shares of common stock or pre-funded warrants have been offered or will be offered pursuant to the offering to the public in the United Kingdom prior to the publication of a prospectus in relation to the shares of common stock or pre-funded warrants which has been approved by the Financial Conduct Authority, except that the shares of common stock or pre-funded warrants may be offered to the public in the United Kingdom at any time:

- a) to any legal entity which is a qualified investor as defined under Article 2 of the U.K. Prospectus Regulation;
- b) to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the U.K. Prospectus Regulation), subject to obtaining the prior consent of the representatives for any such offer; or
- c) in any other circumstances falling within Section 86 of the Financial Services and Markets Act 2000, as amended (FSMA);

provided that no such offer of the shares of common stock or pre-funded warrants shall require us or any underwriter to publish a prospectus pursuant to Section 85 of the FSMA or supplement a prospectus pursuant to Article 23 of the U.K. Prospectus Regulation. For the purposes of this provision, the expression an “offer to the public” in relation to the shares of common stock or pre-funded warrants in the United Kingdom means the communication in any form and by any means of sufficient information on the terms of the offer and any shares of common stock or pre-funded warrants to be offered so as to enable an investor to decide to purchase or subscribe for any shares of common stock or pre-funded warrants and the expression “U.K. Prospectus Regulation” means Regulation (EU) 2017/1129 as it forms part of domestic law by virtue of the European Union (Withdrawal) Act 2018.

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are “qualified investors” (as defined in the U.K. Prospectus Regulation) (i) who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the Order), and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as “relevant persons”) or otherwise in circumstances which have not resulted and will not result in an offer to the public of the shares of common stock or pre-funded warrants in the United Kingdom within the meaning of the FSMA. In the United Kingdom, any investment or investment activity to which this document relates is only available to, and will be engaged in with, relevant persons. Any person in the UK who is not a relevant person must not act on or rely upon this document or any of its contents.

Canada

The shares of common stock or pre-funded warrants may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in

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National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the shares of common stock or pre-funded warrants must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Hong Kong

The shares of common stock or pre-funded warrants have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to "professional investors" as defined in the Securities and Futures Ordinance (Cap. 571 of the Laws of Hong Kong) (the SFO), of Hong Kong and any rules made thereunder; or (b) in other circumstances which do not result in the document being a "prospectus" as defined in the Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32) of Hong Kong (the CO), or which do not constitute an offer to the public within the meaning of the CO. No advertisement, invitation or document relating to the shares of common stock or pre-funded warrants has been or may be issued or has been or may be in the possession of any person for the purposes of issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to shares of common stock or pre-funded warrants which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" as defined in the SFO and any rules made thereunder.

Singapore

The representatives have acknowledged that this prospectus supplement and the accompanying prospectus have not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, the representatives have represented and agreed that it has not offered or sold any shares of common stock or pre-funded warrants or caused the shares of common stock or pre-funded warrants to be made the subject of an invitation for subscription or purchase and will not offer or sell any shares of common stock or pre-funded warrants or cause the shares of common stock or pre-funded warrants to be made the subject of an invitation for subscription or purchase, and has not circulated or distributed, nor will it circulate or distribute, this prospectus supplement and the accompanying prospectus or any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares of common stock or pre-funded warrants, whether directly or indirectly, to any person in Singapore other than:

- a) to an institutional investor (as defined in Section 4A of the Securities and Futures Act (Chapter 289) of Singapore, as modified or amended from time to time (the SFA)) pursuant to Section 274 of the SFA;
- b) to a relevant person (as defined in Section 275(2) of the SFA) pursuant to Section 275(1) of the SFA, or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions specified in Section 275 of the SFA; or
- c) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

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Where the shares of common stock or pre-funded warrants are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

- a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

securities or securities-based derivatives contracts (each term as defined in Section 2(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares of common stock or pre-funded warrants pursuant to an offer made under Section 275 of the SFA except:

- i. to an institutional investor or to a relevant person, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;
- ii. where no consideration is or will be given for the transfer;
- iii. where the transfer is by operation of law;
- iv. as specified in Section 276(7) of the SFA; or
- v. as specified in Regulation 37A of the Securities and Futures (Offers of Investments) (Securities and Securities-based Derivatives Contracts) Regulations 2018

Japan

The shares of common stock or pre-funded warrants have not been and will not be registered pursuant to Article 4, Paragraph 1 of the Financial Instruments and Exchange Act. Accordingly, none of the shares of common stock, pre-funded warrants, nor any interest therein may be offered or sold, directly or indirectly, in Japan or to, or for the benefit of, any "resident" of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to or for the benefit of a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Act and any other applicable laws, regulations and ministerial guidelines of Japan in effect at the relevant time.

Notice to Prospective Investors in Switzerland

We have not and will not register with the Swiss Financial Market Supervisory Authority, or FINMA, as a foreign collective investment scheme pursuant to Article 119 of the Federal Act on Collective Investment Scheme of 23 June 2006, as amended, or CISA, and accordingly the securities being offered pursuant to this prospectus have not and will not be approved, and may not be licenseable, with FINMA. Therefore, the securities have not been authorized for distribution by FINMA as a foreign collective investment scheme pursuant to Article 119 CISA and the securities offered hereby may not be offered to the public (as this term is defined in Article 3 CISA) in or from Switzerland. The securities may solely be offered to "qualified investors," as this term is defined in Article 10 CISA, and in the circumstances set out in Article 3 of the Ordinance on Collective Investment Scheme of 22 November 2006, as amended, or CISO, such that there is no public offer. Investors, however, do not benefit from protection under CISA or CISO or supervision by FINMA. This prospectus and any other materials relating to the securities are strictly personal and confidential to each offeree and do not constitute an offer to any other person. This prospectus may only be used by those qualified investors to whom it has been handed out in connection with the offer described herein and may neither directly or indirectly be distributed or made available to any person or entity other than its recipients. It may not be used in connection with any other offer and shall in particular not be copied and/or distributed to the public in Switzerland or from Switzerland.

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This prospectus does not constitute an issue prospectus as that term is understood pursuant to Article 652a and/or 1156 of the Swiss Federal Code of Obligations. We have not applied for a listing of the securities on the SIX Swiss Exchange or any other regulated securities market in Switzerland, and consequently, the information presented in this prospectus does not necessarily comply with the information standards set out in the listing rules of the SIX Swiss Exchange and corresponding prospectus schemes annexed to the listing rules of the SIX Swiss Exchange.

LEGAL MATTERS

The validity of the shares of common stock and pre-funded warrants offered hereby will be passed upon for us by Cooley LLP, New York, New York. Certain legal matters in connection with this offering will be passed upon for the underwriters by Goodwin Procter LLP, New York, New York. As of the date of this prospectus supplement, GC&H Investments, LLC, an entity consisting of current and former partners and associates of Cooley LLP, beneficially holds an aggregate of 41,396 shares of our common stock.

EXPERTS

The financial statements of Taysha Gene Therapies, Inc. as of December 31, 2024 and 2023, and for each of the two years in the period ended December 31, 2024, incorporated by reference in this prospectus supplement by reference to the Company's Annual Report on Form 10-K for the year ended December 31, 2024, have been audited by Deloitte & Touche LLP, an independent registered public accounting firm, as stated in their report. Such financial statements are incorporated by reference in reliance upon the report of such firm given their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at www.sec.gov. Copies of certain information filed by us with the SEC are also available on our website at www.tayshatx.com. Our website is not a part of this prospectus supplement and is not incorporated by reference in this prospectus supplement.

This prospectus supplement is part of a registration statement that we filed with the SEC. The registration statement contains more information than this prospectus supplement and the accompanying prospectus regarding us and the securities, including certain exhibits and schedules. You can obtain a copy of the registration statement from the SEC at the address listed above or from the SEC's internet site.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference in this prospectus supplement and the accompanying prospectus much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus supplement and the accompanying prospectus is considered to be part of this prospectus supplement and the accompanying prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus supplement and the accompanying prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus supplement and the accompanying prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus supplement, the accompanying prospectus or any document previously incorporated by reference have been modified or superseded. This prospectus supplement and the accompanying prospectus incorporate by reference the documents listed below (File No. 001-39536) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) until the offering of the securities under the registration statement is terminated or completed:

- our Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2024, filed with the SEC on February 26, 2025;
- the information specifically incorporated by reference into our 2024 Form 10-K from our definitive proxy statement on [Schedule 14A](#) (other than information furnished rather than filed), filed with the SEC on April 21, 2025;
- our Quarterly Report on [Form 10-Q](#) for the fiscal quarter ended March 31, 2025, filed with the SEC on May 15, 2025;
- our Current Report on Form 8-K filed with the SEC on [May 28, 2025](#) and our Current Report on Form 8-K/A filed with the SEC on [May 29, 2025](#), to the extent the information in such reports is filed and not furnished; and
- the description of our common stock contained in [Exhibit 4.1](#) to our Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, filed on August 12, 2024, and any amendment or report filed with the SEC for the purpose of updating such description.

We will provide to each person, including any beneficial owner, to whom a prospectus supplement 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 supplement but not delivered with the prospectus supplement, 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.

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus.

In accordance with Rule 412 of the Securities Act, any statement contained in a document incorporated by reference herein shall be deemed modified or superseded to the extent that a statement contained herein or in any other subsequently filed document which also is or is deemed to be incorporated by reference herein modifies or supersedes such statement.

PROSPECTUS



\$300,000,000

**Common Stock
Preferred Stock
Debt Securities
Warrants**

From time to time, we may offer and sell up to an aggregate amount of \$300,000,000 of any combination of shares of our common stock, shares of our preferred stock, debt securities and warrants to purchase any of such securities in one or more offerings as described in this prospectus. We may also offer securities as may be issuable upon conversion, redemption, repurchase, exchange or exercise of any securities registered hereunder, including any applicable anti-dilution provisions.

This prospectus provides a general description of the securities we may offer. Each time we offer securities, we will specify in an accompanying prospectus supplement the terms of the securities being offered. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. You should carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as any documents incorporated by reference, before you invest in any of the securities being offered.

We are an “emerging growth company” and “smaller reporting company” under the federal securities laws and, as such, are subject to reduced public company reporting requirements. See “Prospectus Summary—Implications of Being an Emerging Growth Company and Smaller Reporting Company.”

This prospectus may not be used to consummate a sale of any securities unless accompanied by a prospectus supplement.

Our common stock is traded on the Nasdaq Global Select Market under the symbol “TSHA.” On December 12, 2024, the last reported sale price of our common stock was \$2.25 per share. The applicable prospectus supplement will contain information, where applicable, as to any other listing on the Nasdaq Global Select Market or any securities market or other exchange of the securities, if any, covered by the prospectus supplement.

We may sell these securities directly to investors, through agents designated from time to time or to or through underwriters or dealers, on a continuous or delayed basis. For additional information on the methods of sale, you should refer to the section titled “Plan of Distribution” in this prospectus. If any agents or underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such agents or underwriters and any applicable fees, commissions, discounts or over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading “[Risk Factors](#)” on page 6 of this prospectus and in any applicable prospectus supplement and related free writing prospectus, and under similar headings in the other 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 _____, 2024.

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ABOUT THIS PROSPECTUS

This prospectus is a part of a registration statement on Form S-3 that we filed with the U.S. Securities and Exchange Commission, or the SEC, utilizing a “shelf” registration process under the Securities Act of 1933, as amended, or the Securities Act. Under this shelf registration statement, we may offer and sell, either individually or in combination, from time to time in one or more offerings, the securities described in this prospectus up to a total aggregate offering price of \$300,000,000.

This prospectus provides you with a general description of the securities we may offer. Each time we offer securities under this prospectus, we will provide a prospectus supplement that will contain specific information about the terms of such securities. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change information contained in this prospectus or in any documents that we have incorporated by reference into this prospectus. You should read this prospectus, any applicable prospectus supplement and any related free writing prospectus, together with the information incorporated herein by reference as described under the heading “Incorporation of Certain Information by Reference,” before investing in any of the securities offered.

THIS PROSPECTUS MAY NOT BE USED TO CONSUMMATE A SALE OF SECURITIES UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.

Neither we, nor any agent, underwriter or dealer has authorized any person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus, any applicable prospectus supplement or any related free writing prospectus prepared by or on behalf of us or to which we have referred you. This prospectus, any applicable supplement to this prospectus or any related free writing prospectus do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus, any applicable supplement to this prospectus or any related free writing prospectus constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction.

You should not assume that the information contained in this prospectus, any applicable prospectus supplement or any related free writing prospectus is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus, any applicable prospectus supplement or any related free writing prospectus is delivered, or securities are sold, on a later date.

This prospectus and the information incorporated herein by reference contain summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described below under the heading “Where You Can Find More Information.”

As used in this prospectus, unless the context otherwise requires, references to “we,” “us,” “our,” “the company,” “Taysha” and “Taysha Gene Therapies” refer 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 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 from this prospectus and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the risks of investing in our securities discussed under the heading “Risk Factors” contained in the 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. You should also carefully read the information incorporated by reference into this prospectus, including our financial statements and related notes, and the exhibits to the registration statement of which this prospectus is a part, before making your investment decision.

Overview

We are a clinical-stage biotechnology company focused on advancing adeno-associated virus (AAV)-based gene therapies for the treatment of severe monogenic diseases of the central nervous system, or CNS. Our lead clinical program TSHA-102 is in development for the treatment of Rett syndrome, a rare neurodevelopmental disorder with no approved disease-modifying therapies that address the genetic root cause of the disease. With a singular focus on developing transformative medicines, we aim to address severe unmet medical needs and dramatically improve the lives of patients and their caregivers. Our management team has proven experience in gene therapy development and commercialization. We leverage this experience, our manufacturing process and a clinically and commercially proven AAV9 capsid in an effort to rapidly translate treatments from bench to bedside.

We are evaluating TSHA-102 in the REVEAL Phase 1/2 adolescent and adult trial, which is a first-in-human, open-label, randomized, dose-escalation and dose-expansion study evaluating the safety and preliminary efficacy of TSHA-102 in adolescent and adult females aged 12 years and older with Rett syndrome due to *MECP2* loss-of-function mutation. We are also evaluating TSHA-102 in the REVEAL Phase 1/2 pediatric trial, which is an open-label, randomized, dose-escalation and dose-expansion study evaluating the safety and preliminary efficacy of TSHA-102 in pediatric females with Rett syndrome due to *MECP2* loss-of-function mutation.

We have received Orphan Drug Designation and Rare Pediatric Disease designation from the United States Food and Drug Administration, or FDA, and Orphan Drug Designation from the European Commission for TSHA-102 for the treatment of Rett syndrome. We also received Fast Track designation from the FDA for TSHA-102 for the treatment of Rett syndrome. We also received Clinical Trial Application clearance from the United Kingdom’s Medicines and Healthcare products Regulatory Agency, or U.K. MHRA, in early 2024 for pediatric patients with Rett syndrome. In February 2024, we received Innovative Licensing and Access Pathway, or ILAP, designation for TSHA-102 from the U.K. MHRA. In April 2024, the FDA granted Regenerative Medicine Advanced Therapy, or RMAT, designation for TSHA-102 in Rett syndrome.

We are focused on discovering, developing and commercializing gene therapies for the treatment of monogenic diseases of the CNS, in both rare and large patient populations. Our primary focus is advancing our lead TSHA-102 clinical program in Rett syndrome, while our pipeline of CNS programs offers the potential for additional development opportunities in the future. The stage of development of our Rett syndrome program, including the progress in our ongoing clinical trials, is represented in the below table:



Corporate 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 a part of or 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” as defined in the Securities Exchange Act of 1934, as amended, or the Exchange Act, and 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 Securities We May Offer

We may offer shares of our common stock and preferred stock, various series of debt securities and/or warrants to purchase any of such securities, either individually or in combination, up to a total aggregate amount of \$300,000,000 from time to time in one or more offerings under this prospectus, together with any applicable prospectus supplement and any related free writing prospectus, at prices and on terms to be determined by market conditions at the time of the relevant offering. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

- designation or classification;
- aggregate principal amount or aggregate offering price;
- maturity, if applicable;
- original issue discount, if any;
- rates and times of payment of interest or dividends, if any;
- redemption, conversion, exchange or sinking fund terms, if any;
- conversion or exchange prices or rates, if any, and, if applicable, any provisions for changes to or adjustments in the conversion or exchange prices or rates and in the securities or other property receivable upon conversion or exchange;
- ranking, if applicable;
- restrictive covenants, if any;
- voting or other rights, if any; and
- material U.S. federal income tax considerations.

The applicable prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change information contained in this prospectus or in documents we have incorporated by reference. However, no prospectus supplement or free writing prospectus will offer a security that is not registered and described in this prospectus at the time of the effectiveness of the registration statement of which this prospectus is a part.

This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.

We may sell the securities directly to investors or through underwriters, dealers or agents. We, and our underwriters or agents, reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities through underwriters or agents, we will include in the applicable prospectus supplement:

- the names of those underwriters or agents;
- applicable fees, discounts and commissions to be paid to them;
- details regarding over-allotment options, if any; and
- the estimated net proceeds to us.

Common Stock. We may issue shares of our common stock from time to time. Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. Holders of common stock are entitled to receive ratably any dividends as may be declared by our board of directors, subject to any preferential dividend rights of any series of preferred stock that we may designate and issue in the future.

In the event of our liquidation, dissolution or winding up, the holders of common stock are entitled to receive ratably our net assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock. Holders of common stock have no preemptive, subscription, redemption or conversion rights. There are no redemption or sinking fund provisions applicable to the common stock. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Preferred Stock. We may issue shares of our preferred stock from time to time, in one or more series. Under our certificate of incorporation, our board of directors has the authority, without further action by the stockholders, to issue up to 10,000,000 shares of preferred stock, par value \$0.00001 per share. You should refer to our certificate of incorporation, as amended, and our bylaws, both of which are included as exhibits to documents incorporated by reference in the registration statement of which this prospectus is a part.

Our board of directors may, without further action by our stockholders, from time to time, direct the issuance of shares of preferred stock in series and may, at the time of issuance, determine the rights, preferences and limitations of each series, including voting rights, dividend rights and redemption and liquidation preferences. Satisfaction of any dividend preferences of outstanding shares of preferred stock would reduce the amount of funds available for the payment of dividends on shares of our common stock. Holders of shares of preferred stock may be entitled to receive a preference payment in the event of any liquidation, dissolution or winding-up of our company before any payment is made to the holders of shares of our common stock. In some circumstances, the issuance of shares of preferred stock may render more difficult or tend to discourage a merger, tender offer or proxy contest, the assumption of control by a holder of a large block of our securities or the removal of incumbent management. Upon the affirmative vote of our board of directors, without stockholder approval, we may issue shares of preferred stock with voting and conversion rights which could adversely affect the holders of shares of our common stock.

If we offer a specific series of preferred stock under this prospectus, we will describe the terms of the preferred stock in the prospectus supplement for such offering and will file a copy of the certificate of designation establishing the terms of the preferred stock with the SEC. We urge you to read the applicable prospectus supplement (and any free writing prospectus that we may authorize to be provided to you) related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

Debt Securities. We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. The senior debt securities will rank equally with any other unsecured and unsubordinated debt. The subordinated debt securities will be subordinate and junior in right of payment, to the extent and in the manner described in the instrument governing the debt, to all of our senior indebtedness. Convertible debt securities will be convertible into or exchangeable for our common stock or other securities. Conversion may be mandatory or at the holder's option and would be at prescribed conversion rates.

Any debt securities issued under this prospectus will be issued under one or more documents called indentures, which are contracts between us and a national banking association or other eligible party, as trustee. In this prospectus, we have summarized certain general features of the debt securities. We urge you, however, to read the applicable prospectus supplement (and any free writing prospectus that we may authorize to be provided to you) related to the series of debt securities being offered, as well as the complete indentures that contain the terms of the debt securities. A form of indenture has been filed as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

Warrants. We may issue warrants for the purchase of common stock, preferred stock and/or debt securities in one or more series. We may issue warrants independently or together with common stock, preferred stock and/or debt securities, and the warrants may be attached to or separate from these securities. In this prospectus, we have summarized certain general features of the warrants. We urge you, however, to read the applicable prospectus supplement (and any free writing prospectus that we may authorize to be provided to you) related to the particular series of warrants being offered, as well as the complete warrant agreements and warrant certificates that contain the terms of the warrants. Forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants that may be offered have been filed as exhibits to the registration statement of which this prospectus is a part, and supplemental warrant agreements and forms of warrant certificates will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

Any warrants issued under this prospectus will be evidenced by warrant certificates. Warrants may be issued under an applicable warrant agreement that we enter into with a warrant agent. We will indicate the name and address of the warrant agent, if applicable, in the prospectus supplement relating to the particular series of warrants being offered.

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully review the risks and uncertainties described under the heading “Risk Factors” contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in our most recent Annual Report on Form 10-K, as updated by our subsequent quarterly and other reports and documents that are incorporated by reference into this prospectus and the applicable prospectus supplement, before deciding whether to purchase any of the securities being registered pursuant to the registration statement of which this prospectus is a part. Each of the risk factors described in the documents referenced above could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities, and the occurrence of any of these risks might cause you to lose all or part of your investment. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations. This prospectus and the incorporated documents also contain forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including the risks mentioned elsewhere in this prospectus. Please also read carefully the section below titled “Special Note Regarding Forward-Looking Statements.”

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, each applicable prospectus supplement and the information incorporated by reference herein and therein contain forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act, that involve substantial risks and uncertainties.

All statements, other than statements of historical fact, contained in this prospectus, the applicable prospectus supplement, and the information incorporated by reference herein and therein, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. 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.

The forward-looking statements in this prospectus, the accompanying prospectus supplement and the information incorporated by reference herein and therein include, among other things, statements about:

- 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 syndrome 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 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 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;
- the costs of litigation and our expectations regarding the outcome of lawsuits and other claims against us and any regulatory or legal proceedings;
- our ability to identify, recruit and retain key personnel;

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- 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
- our use of cash and other resources, including our expected use of proceeds from any offering under this prospectus.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make due to various factors, including, but not limited to, those set forth under the heading “Risk Factors” in this prospectus, any applicable prospectus supplement, the documents incorporated by reference therein or any free writing prospectus that we may authorize. In addition, our forward-looking statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date the statement is made, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and you are cautioned not to unduly rely upon these statements. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments.

USE OF PROCEEDS

Except as described in any prospectus supplement or in any related free writing prospectus that we may authorize to be provided to you in connection with a specific offering, we currently intend to use the net proceeds from the sale of securities under this prospectus for general corporate purposes, including but not limited to, clinical trial expenses, research and development expenses, general and administrative expenses and capital expenditures. We may also use a portion of the net proceeds to in-license, invest in or acquire businesses, assets or technologies that we believe are complementary to our own, although we have no current plans, commitments or agreements with respect to any acquisitions. As of the date of this prospectus, we cannot specify with certainty all of the particular uses of the net proceeds, if any, from the sale of securities under this prospectus. Accordingly, we will retain broad discretion over the use of such proceeds. We will set forth in the applicable prospectus supplement or free writing prospectus our intended use of the net proceeds received from the sale of any securities sold pursuant to the prospectus supplement or free writing prospectus. Pending the use of the net proceeds as described above, we intend to invest the net proceeds in investment-grade, interest-bearing instruments.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock and provisions of our certificate of incorporation and bylaws are summaries. References to our certificate of incorporation herein refer to our certificate of incorporation as amended to the date of this prospectus. You should also refer to the certificate of incorporation (including the certificate of amendment thereto) and the bylaws, which are filed as exhibits to our most recent Annual Report on Form 10-K and are incorporated by reference herein.

General

Our certificate of incorporation authorizes us to issue up to 400,000,000 shares of common stock, \$0.00001 par value per share, and 10,000,000 shares of preferred stock, \$0.00001 par value per share. Our board of directors may establish the rights and preferences of the preferred stock from time to time. As of September 30, 2024, we had outstanding 204,943,306 shares of common stock and no shares of preferred stock outstanding.

Common Stock

Voting Rights

Each holder of our common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors. The affirmative vote of holders of at least 66 2/3% of the voting power of all of the then-outstanding shares of capital stock, voting as a single class, is required to amend certain provisions of our certificate of incorporation, including provisions relating to amending the Company's bylaws, the classified board, the size of the Company's board, removal of directors, director liability, vacancies on the Company's board, special meetings, stockholder notices, actions by written consent and exclusive forum.

Dividends

Subject to preferences that may be applicable to any then-outstanding preferred stock, holders of common stock are entitled to receive ratably those dividends, if any, as may be declared from time to time by the board of directors out of legally available funds.

Liquidation

In the event of our liquidation, dissolution or winding up, holders of common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then-outstanding shares of preferred stock.

Rights and Preferences

Holders of common stock have no preemptive, conversion or subscription rights and there are no redemption or sinking fund provisions applicable to the common stock. The rights, preferences and privileges of the holders of common stock are subject to, and may be adversely affected by, the right of the holders of shares of any series of preferred stock that we may designate in the future.

Preferred Stock

Pursuant to our certificate of incorporation, our board of directors has the authority, without further action by our stockholders, from time to time, to designate and issue up to 10,000,000 shares of preferred stock in one or more series, to establish from time to time the number of shares to be included in each such series, to fix the rights, preferences and privileges of the shares of each wholly unissued series and any qualifications, limitations

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or restrictions thereon, and to increase or decrease the number of shares of any such series, but not below the number of shares of such series then outstanding. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of our common stock. The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in control of us and may adversely affect the market price of our common stock and the voting and other rights of the holders of our common stock.

Our board of directors will fix the designations, voting powers, preferences and rights of each series, as well as the qualifications, limitations or restrictions thereof, of the preferred stock of each series that we offer under this prospectus and applicable prospectus supplements in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of that series of preferred stock. This description will include:

- the title and stated value;
- the number of shares we are offering;
- the liquidation preference per share;
- the purchase price per share;
- the dividend rate per share, dividend period and payment dates and method of calculation for dividends;
- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- our right, if any, to defer payment of dividends and the maximum length of any such deferral period;
- the procedures for any auction and remarketing, if any;
- the provisions for a sinking fund, if any;
- the provisions for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;
- any listing of the preferred stock on any securities exchange or market;
- whether the preferred stock will be convertible into our common stock or other securities of ours, including depositary shares and warrants, and, if applicable, the conversion period, the conversion price, or how it will be calculated, and under what circumstances it may be adjusted;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange period, the exchange price, or how it will be calculated, and under what circumstances it may be adjusted;
- voting rights, if any, of the preferred stock;
- preemption rights, if any;
- restrictions on transfer, sale or other assignment, if any;
- whether interests in the preferred stock will be represented by depositary shares;
- a discussion of any material or special U.S. federal income tax considerations applicable to the preferred stock;

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- the relative ranking and preferences of the preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs;
- any limitations on issuances of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock being issued as to dividend rights and rights if we liquidate, dissolve or wind up our affairs; and
- any other specific terms, rights, preferences, privileges, qualifications or restrictions of the preferred stock.

The General Corporation Law of the State of Delaware, or DGCL, the state of our incorporation, provides that the holders of preferred stock will have the right to vote separately as a class (or, in some cases, as a series) on an amendment to our certificate of incorporation if the amendment would change the par value or, unless the certificate of incorporation provided otherwise, the number of authorized shares of the class or change the powers, preferences or special rights of the class or series so as to adversely affect the class or series, as the case may be. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

The issuance of preferred stock could adversely affect the voting power of holders of common stock and reduce the likelihood that common stockholders will receive dividend payments and payments upon liquidation. The issuance could have the effect of decreasing the market price of the common stock. The issuance of preferred stock also could have the effect of delaying, deterring or preventing a change in control of us.

Registration Rights

Astellas Registration Rights

In October 2022, we entered into a registration rights agreement, or the Astellas Registration Rights Agreement, with Astellas Gene Therapies, Inc. (f/k/a Audentes Therapeutics, Inc. (d/b/a Astellas Gene Therapy)), or Astellas, pursuant to which we agreed to register the resale of 7,266,342 shares of our common stock issued and sold to Astellas in a private placement, or the Astellas Shares. We agreed to use reasonable best efforts 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.

In the event sales cannot be made pursuant to the registration statement, subject to certain limited exceptions, we agreed to make pro rata payments to each purchaser as liquidated damages in an amount equal to 1.0% of the aggregate amount paid by the purchaser for the registrable securities then held by the purchaser, per 30-day period or pro rata for any portion thereof for each such 30-day period during which such event continues, subject to certain caps set forth in the Astellas Registration Rights Agreement.

If we propose to register shares of our common stock for our own account or for the account of other stockholders, the holders of Astellas Shares are entitled to notice of the registration and are entitled to include their shares of common stock in the registration statement. These piggyback registration rights are subject to specified conditions and limitations, including the right of the underwriters to limit the number of shares included in any such registration under specified circumstances.

SSI Registration Rights

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. Under the terms of the SSI Securities Purchase Agreement, we agreed to file a registration statement covering the resale of 705,218 shares of our common stock issued and sold to the SSI Investors, or the SSI Shares, and 525,000 shares of

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common stock issuable upon the exercise of outstanding warrants to purchase shares of our common stock, or SSI Warrant Shares, issued and sold to the SSI Investors in a private placement. We agreed to use reasonable best efforts to keep such registration statement continuously effective until the earlier of (i) the date the SSI Shares and SSI 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.

In the event sales cannot be made pursuant to the registration statement, subject to certain limited exceptions, we agreed to make pro rata payments to each purchaser as liquidated damages in an amount equal to 1.0% of the aggregate amount paid by the purchaser for the registrable securities then held by the purchaser, per 30-day period or pro rata for any portion thereof for each such 30-day period during which such event continues, subject to certain caps set forth in the SSI Securities Purchase Agreement.

If we propose to register shares of our common stock for our own account or for the account of other stockholders, the holders of SSI Shares and SSI Warrant Shares are entitled to notice of the registration and are entitled to include their shares of common stock in the registration statement. These piggyback registration rights are subject to specified conditions and limitations, including the right of the underwriters to limit the number of shares included in any such registration under specified circumstances.

2023 Private Placement Registration Rights

In August 2023, we entered into a securities purchase agreement, or the 2023 Purchase Agreement, with certain institutional and other accredited investors, or the PIPE Investors. Under the terms of the 2023 Purchase Agreement, we agreed to prepare and file one or more registration statements to register for resale 122,412,376 shares of our common stock issued and sold to the PIPE Investors and 44,250,978 shares of our common stock issuable upon the exercise of outstanding pre-funded warrants to purchase shares of our common stock issued and sold to the PIPE Investors, collectively the PIPE Shares. 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 PIPE Shares (assuming cashless exercise of the pre-funded warrants) held by or issuable to a Holder (as defined in the 2023 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 is suspended, ceases to remain continuously effective or is unavailable for purchasers to sell registrable securities, subject to certain limited exceptions, we 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 2023 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 2023 Purchase Agreement.

Board Observer Rights

In October 2022, we entered into a securities purchase agreement with Astellas, or the Astellas SPA, pursuant to which Astellas has the right to designate one individual to attend all meetings of the board of directors in a non-voting observer capacity, or the Astellas Board Observer. The Astellas Board Observer is entitled to all notices, minutes, consents and other materials provided to our directors at the same time and in the same manner as provided to such directors. The Astellas Board Observer right terminates upon a Change of Control (as defined in the Astellas SPA) or when Astellas no longer holds shares of our common stock.

In June 2023, our board of directors appointed Paul B. Manning as a non-voting board observer, and in such capacity, Mr. Manning may attend, in a non-voting capacity, all meetings of the Board.

Anti-Takeover Provisions

Section 203 of the DGCL

We are subject to Section 203 of the DGCL, or Section 203, which prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, with the following exceptions:

- before such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction began, excluding for purposes of determining the voting stock outstanding, but not the outstanding voting stock owned by the interested stockholder, those shares owned (i) by persons who are directors and also officers and (ii) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- on or after such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock that is not owned by the interested stockholder.

In general, Section 203 defines a “business combination” to include the following:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;
- subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits by or through the corporation.

In general, Section 203 defines an “interested stockholder” as an entity or person who, together with the person’s affiliates and associates, beneficially owns, or within three years prior to the time of determination of interested stockholder status did own, 15% or more of the outstanding voting stock of the corporation.

Certificate of Incorporation and Bylaws

Our certificate of incorporation provides for our board of directors to be divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. Because our stockholders do not have cumulative voting rights, stockholders holding a majority of the shares of common stock outstanding will be able to elect all of our directors. Our certificate of incorporation and bylaws provide that directors may be removed by the stockholders only for cause upon the vote of 66^{2/3}% or more of our outstanding common stock. Furthermore, the authorized number of directors may be changed only by resolution of the board of directors, and vacancies and newly created directorships on the board of directors may, except as otherwise required by law or determined by the board, only be filled by a majority vote of the directors then serving on the board, even though less than a quorum.

Our certificate of incorporation and bylaws also provide that all stockholder actions must be effected at a duly called meeting of stockholders and will eliminate the right of stockholders to act by written consent without

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a meeting. The bylaws provide that only the Chairman of the board, Chief Executive Officer or the board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors may call a special meeting of stockholders. The bylaws also provide that stockholders seeking to present proposals before a meeting of stockholders to nominate candidates for election as directors at a meeting of stockholders must provide timely advance notice in writing, and will specify requirements as to the form and content of a stockholder's notice.

Our certificate of incorporation and bylaws provide that the stockholders cannot amend many of the provisions described above except by a vote of 66 2/3% or more of our outstanding common stock.

Our certificate of incorporations gives our board of directors the authority, without further action by our stockholders, to issue up to 10,000,000 shares of preferred stock in one or more series, with any rights, preferences and privileges as they may designate, including the right to approve an acquisition or other change in control.

The combination of these provisions will make it more difficult for our existing stockholders to replace our board of directors as well as for another party to obtain control of us by replacing our board of directors. Since our board of directors has the power to retain and discharge our officers, these provisions could also make it more difficult for existing stockholders or another party to effect a change in management. In addition, the authorization of undesignated preferred stock makes it possible for our board of directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to change control of our company.

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to reduce our vulnerability to hostile takeovers and to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and may have the effect of delaying changes in control or management of our company. As a consequence, these provisions may also inhibit fluctuations in the market price of our stock that could result from actual or rumored takeover attempts. We believe that the benefits of these provisions, including increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure our company, outweigh the disadvantages of discouraging takeover proposals, because negotiation of takeover proposals could result in an improvement of their terms.

Choice of Forum

Our certificate of incorporation provides that the Court of Chancery of the state of Delaware will be the exclusive forum for the following types of actions or proceedings under Delaware statutory or common law:

- any derivative action or proceeding brought on our behalf;
- any action asserting a breach of fiduciary duty;
- any action asserting a claim against us arising pursuant to the DGCL, our certificate of incorporation or our bylaws;
- any claim or cause of action seeking to interpret, apply, enforce or determine the validity of our certificate of incorporation or our amended and restated bylaws;
- any claim or cause of action as to which the DGCL confers jurisdiction on the Court of Chancery of the state of Delaware; or
- any action asserting a claim against us that is governed by the internal affairs doctrine.

The provision does not apply to suits brought to enforce a duty or liability created by the Exchange Act or to claims for which the federal courts have exclusive jurisdiction. Furthermore, Section 22 of the Securities Act

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creates concurrent jurisdiction for federal and state courts over all such Securities Act actions. Accordingly, both state and federal courts have jurisdiction to entertain such claims. To prevent having to litigate claims in multiple jurisdictions and the threat of inconsistent or contrary rulings by different courts, among other considerations, our certificate of incorporation also provides that unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States shall be the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. Although our certificate of incorporation contains the choice of forum provision described above, it is possible that a court could rule that such a provision is inapplicable for a particular claim or action or that such provision is unenforceable.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Equiniti Trust Company, LLC (f/k/a American Stock Transfer & Trust Company, LLC), with offices at 55 Challenger Road, Ridgefield Park, NJ 07660. The transfer agent for any series of preferred stock that we may offer under this prospectus will be named and described in the prospectus supplement for that series.

Listing on Nasdaq

Our common stock is listed on the Nasdaq Global Select Market under the symbol "TSHA."

DESCRIPTION OF DEBT SECURITIES

We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. While the terms we have summarized below will apply generally to any debt securities that we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. The terms of any debt securities offered under a prospectus supplement may differ from the terms described below. Unless the context requires otherwise, whenever we refer to the indenture, we also are referring to any supplemental indentures that specify the terms of a particular series of debt securities.

We will issue the debt securities under the indenture that we will enter into with the trustee named in the indenture. The indenture will be qualified under the Trust Indenture Act of 1939, as amended, or the Trust Indenture Act. We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

The following summary of material provisions of the debt securities and the indenture is subject to, and qualified in its entirety by reference to, all of the provisions of the indenture applicable to a particular series of debt securities. We urge you to read the applicable prospectus supplements and any related free writing prospectuses related to the debt securities that we may offer under this prospectus, as well as the complete indenture that contains the terms of the debt securities.

General

The indenture does not limit the amount of debt securities that we may issue. It provides that we may issue debt securities up to the principal amount that we may authorize and may be in any currency or currency unit that we may designate. Except for the limitations on consolidation, merger and sale of all or substantially all of our assets contained in the indenture, the terms of the indenture do not contain any covenants or other provisions designed to give holders of any debt securities protection against changes in our operations, financial condition or transactions involving us.

We may issue the debt securities issued under the indenture as “discount securities,” which means they may be sold at a discount below their stated principal amount. These debt securities, as well as other debt securities that are not issued at a discount, may be issued with “original issue discount,” or OID, for U.S. federal income tax purposes because of interest payment and other characteristics or terms of the debt securities. Material U.S. federal income tax considerations applicable to debt securities issued with OID will be described in more detail in any applicable prospectus supplement.

We will describe in the applicable prospectus supplement the terms of the series of debt securities being offered, including:

- the title of the series of debt securities;
- any limit upon the aggregate principal amount that may be issued;
- the maturity date or dates;
- the form of the debt securities of the series;
- the applicability of any guarantees;
- whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;
- whether the debt securities rank as senior debt, senior subordinated debt, subordinated debt or any combination thereof, and the terms of any subordination;

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- if the price (expressed as a percentage of the aggregate principal amount thereof) at which such debt securities will be issued is a price other than the principal amount thereof, the portion of the principal amount thereof payable upon declaration of acceleration of the maturity thereof, or if applicable, the portion of the principal amount of such debt securities that is convertible into another security or the method by which any such portion shall be determined;
- the interest rate or rates, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the dates interest will be payable and the regular record dates for interest payment dates or the method for determining such dates;
- our right, if any, to defer payment of interest and the maximum length of any such deferral period;
- if applicable, the date or dates after which, or the period or periods during which, and the price or prices at which, we may, at our option, redeem the series of debt securities pursuant to any optional or provisional redemption provisions and the terms of those redemption provisions;
- the date or dates, if any, on which, and the price or prices at which we are obligated, pursuant to any mandatory sinking fund or analogous fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities and the currency or currency unit in which the debt securities are payable;
- the denominations in which we will issue the series of debt securities, if other than denominations of \$1,000 and any integral multiple thereof;
- any and all terms, if applicable, relating to any auction or remarketing of the debt securities of that series and any security for our obligations with respect to such debt securities and any other terms which may be advisable in connection with the marketing of debt securities of that series;
- whether the debt securities of the series shall be issued in whole or in part in the form of a global security or securities; the terms and conditions, if any, upon which such global security or securities may be exchanged in whole or in part for other individual securities and the depositary for such global security or securities;
- if applicable, the provisions relating to conversion or exchange of any debt securities of the series and the terms and conditions upon which such debt securities will be so convertible or exchangeable, including the conversion or exchange price, as applicable, or how it will be calculated and may be adjusted, any mandatory or optional (at our option or the holders' option) conversion or exchange features, the applicable conversion or exchange period and the manner of settlement for any conversion or exchange;
- if other than the full principal amount thereof, the portion of the principal amount of debt securities of the series which shall be payable upon declaration of acceleration of the maturity thereof;
- additions to or changes in the covenants applicable to the particular debt securities being issued, including, among others, the consolidation, merger or sale covenant;
- additions to or changes in the events of default with respect to the securities and any change in the right of the trustee or the holders to declare the principal, premium, if any, and interest, if any, with respect to such securities to be due and payable;
- additions to or changes in or deletions of the provisions relating to covenant defeasance and legal defeasance;
- additions to or changes in the provisions relating to satisfaction and discharge of the indenture;
- additions to or changes in the provisions relating to the modification of the indenture both with and without the consent of holders of debt securities issued under the indenture;
- the currency of payment of debt securities if other than U.S. dollars and the manner of determining the equivalent amount in U.S. dollars;

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- whether interest will be payable in cash or additional debt securities at our or the holders' option and the terms and conditions upon which the election may be made;
- the terms and conditions, if any, upon which we will pay amounts in addition to the stated interest, premium, if any and principal amounts of the debt securities of the series to any holder that is not a "United States person" for federal tax purposes;
- any restrictions on transfer, sale or assignment of the debt securities of the series; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities, any other additions or changes in the provisions of the indenture, and any terms that may be required by us or advisable under applicable laws or regulations.

Conversion or Exchange Rights

We will set forth in the applicable prospectus supplement the terms on which a series of debt securities may be convertible into or exchangeable for our common stock or our other securities. We will include provisions as to settlement upon conversion or exchange and whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or our other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the indenture will not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of our assets as an entirety or substantially as an entirety. However, any successor to or acquirer of such assets (other than a subsidiary of ours) must assume all of our obligations under the indenture or the debt securities, as appropriate.

Events of Default under the Indenture

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the following are events of default under the indenture with respect to any series of debt securities that we may issue:

- if we fail to pay any installment of interest on any series of debt securities, as and when the same shall become due and payable, and such default continues for a period of 90 days; provided, however, that a valid extension of an interest payment period by us in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of interest for this purpose;
- if we fail to pay the principal of, or premium, if any, on any series of debt securities as and when the same shall become due and payable whether at maturity, upon redemption, by declaration or otherwise, or in any payment required by any sinking or analogous fund established with respect to such series; provided, however, that a valid extension of the maturity of such debt securities in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of principal or premium, if any;
- if we fail to observe or perform any other covenant or agreement contained in the debt securities or the indenture, other than a covenant specifically relating to another series of debt securities, and our failure continues for 90 days after we receive written notice of such failure, requiring the same to be remedied and stating that such is a notice of default thereunder, from the trustee or holders of at least 25% in aggregate principal amount of the outstanding debt securities of the applicable series; and
- if specified events of bankruptcy, insolvency or reorganization occur.

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If an event of default with respect to debt securities of any series occurs and is continuing, other than an event of default specified in the last bullet point above, the trustee or the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series, by notice to us in writing, and to the trustee if notice is given by such holders, may declare the unpaid principal of, premium, if any, and accrued interest, if any, due and payable immediately. If an event of default specified in the last bullet point above occurs with respect to us, the principal amount of and accrued interest, if any, of each issue of debt securities then outstanding shall be due and payable without any notice or other action on the part of the trustee or any holder.

The holders of a majority in principal amount of the outstanding debt securities of an affected series may waive any default or event of default with respect to the series and its consequences, except defaults or events of default regarding payment of principal, premium, if any, or interest, unless we have cured the default or event of default in accordance with the indenture. Any waiver shall cure the default or event of default.

Subject to the terms of the indenture, if an event of default under an indenture shall occur and be continuing, the trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, or exercising any trust or power conferred on the trustee, with respect to the debt securities of that series, provided that:

- the direction so given by the holder is not in conflict with any law or the applicable indenture; and
- subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will have the right to institute a proceeding under the indenture or to appoint a receiver or trustee, or to seek other remedies only if:

- the holder has given written notice to the trustee of a continuing event of default with respect to that series;
- the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made written request,
- such holders have offered to the trustee indemnity satisfactory to it against the costs, expenses and liabilities to be incurred by the trustee in compliance with the request; and
- the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the trustee regarding our compliance with specified covenants in the indenture.

Modification of Indenture; Waiver

We and the trustee may change an indenture without the consent of any holders with respect to specific matters:

- to cure any ambiguity, defect or inconsistency in the indenture or in the debt securities of any series;

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- to comply with the provisions described above under “Description of Debt Securities—Consolidation, Merger or Sale;”
- to provide for uncertificated debt securities in addition to or in place of certificated debt securities;
- to add to our covenants, restrictions, conditions or provisions such new covenants, restrictions, conditions or provisions for the benefit of the holders of all or any series of debt securities, to make the occurrence, or the occurrence and the continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default or to surrender any right or power conferred upon us in the indenture;
- to add to, delete from or revise the conditions, limitations, and restrictions on the authorized amount, terms, or purposes of issue, authentication and delivery of debt securities, as set forth in the indenture;
- to make any change that does not adversely affect the interests of any holder of debt securities of any series in any material respect;
- to provide for the issuance of and establish the form and terms and conditions of the debt securities of any series as provided above under “Description of Debt Securities—General” to establish the form of any certifications required to be furnished pursuant to the terms of the indenture or any series of debt securities, or to add to the rights of the holders of any series of debt securities;
- to evidence and provide for the acceptance of appointment under any indenture by a successor trustee; or
- to comply with any requirements of the SEC in connection with the qualification of any indenture under the Trust Indenture Act.

In addition, under the indenture, the rights of holders of a series of debt securities may be changed by us and the trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series that is affected. However, unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, we and the trustee may make the following changes only with the consent of each holder of any outstanding debt securities affected:

- extending the fixed maturity of any debt securities of any series;
- reducing the principal amount, reducing the rate of or extending the time of payment of interest, or reducing any premium payable upon the redemption of any series of any debt securities; or
- reducing the percentage of debt securities, the holders of which are required to consent to any amendment, supplement, modification or waiver.

Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for specified obligations, including obligations to:

- provide for payment;
- register the transfer or exchange of debt securities of the series;
- replace stolen, lost or mutilated debt securities of the series;
- pay principal of and premium and interest on any debt securities of the series;
- maintain paying agencies;
- hold monies for payment in trust;
- recover excess money held by the trustee;
- compensate and indemnify the trustee; and
- appoint any successor trustee.

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In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, any premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we provide otherwise in the applicable prospectus supplement, in denominations of \$1,000 and any integral multiple thereof. The indenture provides that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company, or DTC, or another depository named by us and identified in the applicable prospectus supplement with respect to that series. To the extent the debt securities of a series are issued in global form and as book-entry, a description of terms relating to any book-entry securities will be set forth in the applicable prospectus supplement.

At the option of the holder, subject to the terms of the indenture and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indenture and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange, we will impose no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or
- register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Trustee

The trustee, other than during the occurrence and continuance of an event of default under an indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the trustee is under no obligation to exercise any of the powers given it by the indenture at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, we will make interest payments by check that we will mail to the holder or by wire transfer to certain holders. Unless we otherwise indicate in the applicable prospectus supplement, we will designate the corporate trust office of the trustee as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the trustee for the payment of the principal of or any premium or interest on any debt securities that remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the debt security thereafter may look only to us for payment thereof.

Governing Law

The indenture and the debt securities will be governed by and construed in accordance with the internal laws of the State of New York, except to the extent that the Trust Indenture Act of 1939 is applicable.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplement and free writing prospectus, summarizes the material terms and provisions of the warrants that we may offer under this prospectus, which may consist of warrants to purchase common stock, preferred stock or debt securities and may be issued in one or more series. Warrants may be offered independently or together with common stock, preferred stock or debt securities offered by any prospectus supplement, and may be attached to or separate from those securities. While the terms we have summarized below will apply generally to any warrants that we may offer under this prospectus, we will describe the particular terms of any series of warrants that we may offer in more detail in the applicable prospectus supplement and any applicable free writing prospectus. The terms of any warrants offered under a prospectus supplement may differ from the terms described below. However, no prospectus supplement will fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness.

We have filed forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants that may be offered as exhibits to the registration statement of which this prospectus is a part. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of warrant agreement, if any, including a form of warrant certificate, that describes the terms of the particular series of warrants we are offering. The following summaries of material provisions of the warrants and the warrant agreements are subject to, and qualified in their entirety by reference to, all the provisions of the warrant agreement and warrant certificate applicable to the particular series of warrants that we may offer under this prospectus. We urge you to read the applicable prospectus supplements related to the particular series of warrants that we may offer under this prospectus, as well as any related free writing prospectuses, and the complete warrant agreements and warrant certificates that contain the terms of the warrants.

General

We will describe in the applicable prospectus supplement the terms relating to a series of warrants being offered, including, to the extent applicable:

- the title of such securities;
- the offering price or prices and aggregate number of warrants offered;
- the currency or currencies for which the warrants may be purchased;
- if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;
- if applicable, the date on and after which the warrants and the related securities will be separately transferable;
- if applicable, the minimum or maximum amount of such warrants which may be exercised at any one time;
- in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at which, and currency in which, this principal amount of debt securities may be purchased upon such exercise;
- in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which, and the currency in which, these shares may be purchased upon such exercise;
- the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreements and the warrants;

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- the terms of any rights to redeem or call the warrants;
- the terms of any rights to force the exercise of the warrants;
- any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;
- the dates on which the right to exercise the warrants will commence and expire;
- the manner in which the warrant agreements and warrants may be modified;
- a discussion of any material or special U.S. federal income tax consequences of holding or exercising the warrants;
- the terms of the securities issuable upon exercise of the warrants; and
- any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including:

- in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture; or
- in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

Exercise of Warrants

Each warrant will entitle the holder to purchase the securities that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants at any time up to the specified time on the expiration date that we set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants by delivering the warrant certificate representing the warrants to be exercised together with specified information, and paying the required amount to the warrant agent in immediately available funds, as provided in the applicable prospectus supplement. We will set forth on the reverse side of the warrant certificate and in the applicable prospectus supplement the information that the holder of the warrant will be required to deliver to the warrant agent in connection with the exercise of the warrant.

Upon receipt of the required payment and the warrant certificate properly completed and duly executed at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement, we will issue and deliver the securities purchasable upon such exercise. If fewer than all of the warrants represented by the warrant certificate are exercised, then we will issue a new warrant certificate for the remaining amount of warrants. If we so indicate in the applicable prospectus supplement, holders of the warrants may surrender securities as all or part of the exercise price for warrants.

Governing Law

Unless we provide otherwise in the applicable prospectus supplement, the warrants and warrant agreements, and any claim, controversy or dispute arising under or related to the warrants or warrant agreements, will be governed by and construed in accordance with the laws of the State of New York.

Enforceability of Rights by Holders of Warrants

Each warrant agent will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust company may act as warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the securities purchasable upon exercise of, its warrants.

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that we or any applicable trustee, depository or warrant agent maintain for this purpose as the “holders” of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as “indirect holders” of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

Book-Entry Holders

We may issue securities in book-entry form only, as we will specify in the applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depository on behalf of other financial institutions that participate in the depository’s book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Global securities will be registered in the name of the depository or its participants. Consequently, for global securities, we will recognize only the depository as the holder of the securities, and we will make all payments on the securities to the depository. The depository passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depository and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a global security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depository’s book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not legal holders, of the securities.

Street Name Holders

A global security may be terminated in certain situations as described under “—Special Situations When a Global Security Will Be Terminated,” or issue securities that are not issued in global form. In these cases, investors may choose to hold their securities in their own names or in “street name.” Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we or any applicable trustee or depository will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we or any such trustee or depository will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not legal holders, of those securities.

Legal Holders

Our obligations, as well as the obligations of any applicable trustee or third party employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form.

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For example, once we make a payment or give a notice to the legal holder, we have no further responsibility for the payment or notice even if that legal holder is required, under agreements with its participants or customers or by law, to pass it along to the indirect holders but does not do so. Similarly, we may want to obtain the approval of the holders to amend an indenture, to relieve us of the consequences of a default or of our obligation to comply with a particular provision of an indenture, or for other purposes. In such an event, we would seek approval only from the legal holders, and not the indirect holders, of the securities. Whether and how the legal holders contact the indirect holders is up to the legal holders.

Special Considerations for Indirect Holders

If you hold securities through a bank, broker or other financial institution, either in book-entry form because the securities are represented by one or more global securities or in street name, you should check with your own institution to find out:

- how it handles securities payments and notices;
- whether it imposes fees or charges;
- how it would handle a request for the holders' consent, if ever required;
- whether and how you can instruct it to send you securities registered in your own name so you can be a holder, if that is permitted in the future;
- how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and
- if the securities are in book-entry form, how the depositary's rules and procedures will affect these matters.

Global Securities

A global security is a security that represents one or any other number of individual securities held by a depositary. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we issue to, deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depositary. Unless we specify otherwise in the applicable prospectus supplement, the DTC will be the depositary for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depositary, its nominee or a successor depositary, unless special termination situations arise. We describe those situations below under “—Special Situations When a Global Security Will Be Terminated.” As a result of these arrangements, the depositary, or its nominee, will be the sole registered owner and legal holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depositary or with another institution that does. Thus, an investor whose security is represented by a global security will not be a legal holder of the security, but only an indirect holder of a beneficial interest in the global security.

If the prospectus supplement for a particular security indicates that the security will be issued as a global security, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

Special Considerations for Global Securities

As an indirect holder, an investor's rights relating to a global security will be governed by the account rules of the investor's financial institution and of the depositary, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depositary that holds the global security.

If securities are issued only as global securities, an investor should be aware of the following:

- an investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;
- an investor will be an indirect holder and must look to his or her own bank or broker for payments on the securities and protection of his or her legal rights relating to the securities, as we describe above;
- an investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;
- an investor may not be able to pledge his or her interest in the global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;
- the depositary's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in the global security;
- we and any applicable trustee have no responsibility for any aspect of the depositary's actions or for its records of ownership interests in the global security, nor will we or any applicable trustee supervise the depositary in any way;
- the depositary may, and we understand that DTC will, require that those who purchase and sell interests in the global security within its book-entry system use immediately available funds, and your broker or bank may require you to do so as well; and
- financial institutions that participate in the depositary's book-entry system, and through which an investor holds its interest in the global security, may also have their own policies affecting payments, notices and other matters relating to the securities.

There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

Special Situations When a Global Security Will Be Terminated

In a few special situations described below, a global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks or brokers to find out how to have their interests in securities transferred to their own names, so that they will be direct holders. We have described the rights of holders and street name investors above.

Unless we provide otherwise in the applicable prospectus supplement, the global security will terminate when the following special situations occur:

- if the depositary notifies us that it is unwilling, unable or no longer qualified to continue as depositary for that global security and we do not appoint another institution to act as depositary within 90 days;
- if we notify any applicable trustee that we wish to terminate that global security; or
- if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

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The applicable prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by the prospectus supplement. When a global security terminates, the depository, and neither we nor any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

PLAN OF DISTRIBUTION

We may sell the securities from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods. We may sell the securities to or through underwriters or dealers, through agents, or directly to one or more purchasers. We may distribute securities from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

We may also sell equity securities covered by this registration statement in an “at the market offering” as defined in Rule 415(a)(4) under the Securities Act. Such offering may be made into an existing trading market for such securities in transactions at other than a fixed price on or through the facilities of the Nasdaq Global Select Market or any other securities exchange or quotation or trading service on which such securities may be listed, quoted or traded at the time of sale. Such at the market offerings, if any, may be conducted by underwriters acting as principal or agent.

A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the securities, including, to the extent applicable:

- the name or names of any underwriters, dealers or agents, if any;
- the purchase price of the securities and the proceeds we will receive from the sale;
- any over-allotment options under which underwriters may purchase additional securities from us;
- any agency fees or underwriting discounts and other items constituting agents’ or underwriters’ compensation;
- any public offering price;
- any discounts or concessions allowed or reallocated or paid to dealers; and
- any securities exchange or market on which the securities may be listed.

Only underwriters named in the prospectus supplement are underwriters of the securities offered by the prospectus supplement.

If underwriters are used in the sale, they will acquire the securities for their own account and may resell the securities from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the securities will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the securities to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all of the securities offered by the prospectus supplement, other than securities covered by any over-allotment or other option. Any public offering price and any discounts or concessions allowed or reallocated or paid to dealers may change from time to time. We may use underwriters with whom we have a material relationship. We will describe in the prospectus supplement, naming the underwriter, the nature of any such relationship.

We may sell securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities, and we will describe any commissions and other compensation we will pay the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

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We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

We may provide agents and underwriters with indemnification against civil liabilities related to this offering, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities. Agents and underwriters may engage in transactions with, or perform services for, us in the ordinary course of business.

All securities we may offer, other than common stock, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

Any underwriter may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids. Overallotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the securities in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a stabilizing or covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time. These transactions may be effected on any exchange or over-the-counter market or otherwise.

Any underwriters or agents who are qualified market makers on the Nasdaq Global Select Market may engage in passive market making transactions in the securities on the Nasdaq Global Select Market in accordance with Rule 103 of Regulation M under the Exchange Act, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the securities. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded. Passive market making may stabilize the market price of the securities at a level above that which might otherwise prevail in the open market and, if commenced, may be discontinued at any time.

In compliance with guidelines of the Financial Industry Regulatory Authority, or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and the applicable prospectus supplement.

The specific terms of any lock-up provisions with respect to any given offering will be described in the applicable prospectus supplement.

LEGAL MATTERS

Unless otherwise indicated in the applicable prospectus supplement, certain legal matters in connection with the offering and the validity of the securities offered by this prospectus, and any supplement thereto, will be passed upon by Cooley LLP, New York, New York. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement. 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 41,396 shares of our common stock.

EXPERTS

The financial statements incorporated by reference in this prospectus have been audited by Deloitte & Touche LLP, an independent registered public accounting firm, as stated in their report. Such financial statements are incorporated by reference in reliance upon the report of such firm, given upon their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE 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. Neither we nor any agent, underwriter or dealer has authorized any person 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 fiscal year ended December 31, 2023, filed with the SEC on March 19, 2024;
- the information specifically incorporated by reference into our Annual Report on [Form 10-K](#) for the year ended December 31, 2023 from our Definitive Proxy Statement on [Schedule 14A](#), filed with the SEC on April 18, 2024;
- our Quarterly Reports on Form 10-Q for the fiscal quarters ended [March 31, 2024](#), [June 30, 2024](#) and [September 30, 2024](#), filed with the SEC on May 14, 2024, August 12, 2024 and November 13, 2024, respectively;
- our Current Reports on Form 8-K filed with the SEC on [May 30, 2024](#), [June 26, 2024](#) and [June 26, 2024](#) to the extent the information in such reports is filed and not furnished; and
- the description of our common stock contained in [Exhibit 4.1](#) to our Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, filed on August 12, 2024, and any amendment or report filed with the SEC for the purpose of updating such 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.



**46,868,687 Shares of Common Stock
Pre-Funded Warrants to Purchase up to 25,858,586 Shares of Common Stock**

Jefferies

BofA Securities

Piper Sandler

Barclays

Prospectus Supplement dated May 28, 2025
