

Corporate Presentation

May 2024

Legal disclosure

FORWARD LOOKING STATEMENTS

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are subject to a number of risks, uncertainties and assumptions. Risks regarding our business are described in detail in our Securities and Exchange Commission filings, including in our Annual Report on Form 10-K for the year ended December 31, 2023, and our other filings with the SEC, which are available on the SEC’s website at www.sec.gov. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law.

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

Key investment highlights

TSHA-102: Lead Clinical Program in Rett Syndrome

- Ongoing REVEAL Phase 1/2 adolescent and adult trial (Canada, U.S.) and ongoing REVEAL Phase 1/2 pediatric trial (U.S., U.K.)
- Novel miRARE technology designed to mediate *MECP2* expression on a cell-by-cell basis (enables protein production in *MECP2*-deficient cells, silences transgene expression in healthy cells) to address risks associated with under- and over-expression of *MECP2*
- High unmet medical need and significant market opportunity of 15,000-20,000 (U.S., EU+U.K.)¹ with typical Rett syndrome caused by a *MECP2* mutation
- Potential to obtain Priority Review Voucher (PRV)

Transformative Potential

- Data from two adult patients dosed support TSHA-102 was generally well-tolerated with no treatment-emergent SAEs
- Sustained and new improvements demonstrated across key efficacy measures and multiple clinical domains
- Similar patterns of response observed in both adult patients with different genetic mutations and phenotypic expression

Proven and Well- Characterized Delivery

- Clinically and commercially proven AAV9 capsid with clinical activity and tolerability across multiple CNS indications
- Intrathecal delivery in an outpatient setting targets key CNS regions and minimizes viral load, potentially reducing risk of systemic inflammatory response
- Self-complementary technology facilitates more rapid transgene expression

Well-Capitalized

- \$150 million private placement from new and existing investors along with cash and cash equivalents expected to extend cash runway into 2026

Proven Leadership

- Led by former AveXis management, who developed and launched ZOLGENSMA, the second one-time gene therapy FDA approved
- Strong relationships with key gene therapy stakeholders, including regulatory authorities, suppliers and other third parties

Near-Term Catalysts

- Mid-2024 – Expect initial clinical data from cohort one (low dose, 5.7×10^{14} total vg) in REVEAL Phase 1/2 pediatric trial
- 2H 2024 – Expect initial clinical data from cohort two (high dose, 1×10^{15} total vg) in both the adolescent/adult and pediatric REVEAL trials

Progress in clinical-stage TSHA-102 program supports clinical evaluation across a broad range of ages and stages of Rett syndrome

REVEAL Phase 1/2 Adolescent & Adult Trial *in U.S. and Canada*

- ✓ Completed dosing of cohort one (low dose, n=2); encouraging longer-term safety and efficacy data*
- ✓ Presented initial clinical data from the first two adult patients at the BPNA 2024 Annual Conference
- ✓ Health Canada authorized protocol amendment to include patients ≥12 years of age
- ✓ Received IDMC approval of Company's request to proceed to high dose cohort earlier than planned
- ✓ Trial now expanding into the U.S. following submission of 12+ protocol to U.S. FDA
- ✓ ODD, RPDD, FTD and RMAT from U.S. FDA

REVEAL Phase 1/2 Pediatric Trial *in U.S. and U.K.*

- ✓ U.S. FDA cleared IND for TSHA-102
- ✓ Dosed first pediatric patient in the U.S.
- ✓ Received IDMC approval to dose second patient in cohort one (low dose)
- ✓ U.K. MHRA authorized CTA for TSHA-102
- ✓ ODD, RPDD, FTD and RMAT from U.S. FDA, ODD from EU EMA and ILAP designation from U.K. MHRA

2024: significant clinical data generation expected in adult, adolescent and pediatric patients across multiple geographies

Rett syndrome: a rare, progressive X-linked neurodevelopmental disease

- Caused by mutations in the X-linked MECP2 gene, a critical transcriptional regulator required for proper neuronal development and brain function¹
- Mutations in MECP2 inhibit neuronal development, leading to impaired brain development and function¹
- Primarily occurs in females
- Female heterozygous patients are mosaic carriers of normal and mutated MECP2, and symptoms and severity vary, due in part to random X-inactivation²

Rett syndrome is divided into four key stages³



STAGE I

Developmental Arrest

6-18 months (typical)
≤6 months (early)

Symptom onset



STAGE II

Rapid Deterioration

1-4 years

Symptom progression



STAGE III

Pseudo Stationary

4-10 years

Symptom stabilization



STAGE IV

Late Motor Deterioration

>10 years

Muscle wasting with age

Hallmark characteristics of Rett syndrome appear across multiple clinical domains impacting activities of daily living

The cortical architecture and function abnormalities observed across the CNS in Rett syndrome can have a significant impact on motor function, socialization and autonomic function

Gross Motor Function	Fine Motor Function	Socialization / Communication	Autonomic Function
<ul style="list-style-type: none">○ Mobility issues○ Loss of movement and coordination abilities○ Gait disturbances○ Hypotonia○ Dystonia	<ul style="list-style-type: none">○ Loss of hand function○ Loss of purposeful hand use○ Repetitive hand movements	<ul style="list-style-type: none">○ Loss of speech/communication○ Social withdraw○ Behavioral issues○ Intellectual disability	<ul style="list-style-type: none">○ Seizures*○ Sleep disturbances○ Breathing issues○ Gastrointestinal issues○ Cardiac function○ Vasomotor disturbances

**seizures can be caused by other etiologies*

No approved disease-modifying treatments address the genetic root cause of Rett syndrome

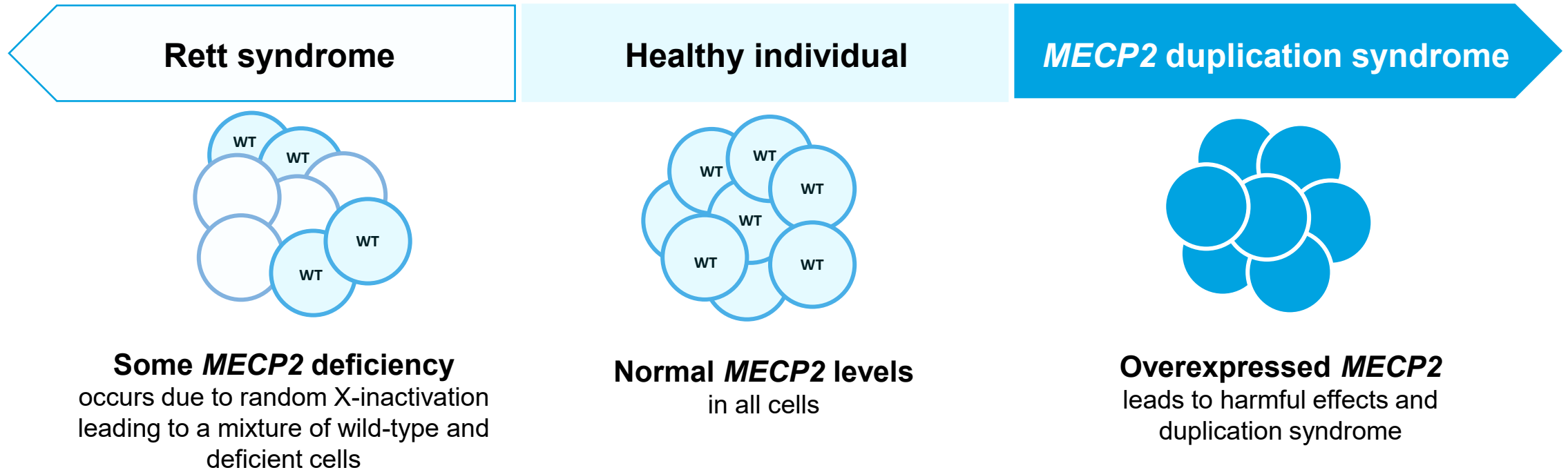
High unmet medical need

- Current standard of care focused on symptom management²
- High caregiver burden and significant impact on quality of life

Significant market opportunity

- Estimated prevalence of typical Rett syndrome caused by a *MECP2* mutation is between **15,000 and 20,000** in major global markets (U.S., EU+U.K.)¹
- Rett syndrome occurs worldwide in **1 of every 10,000** female births¹

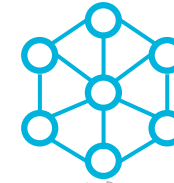
Gene Therapy Challenge: too much or too little *MECP2* expression is harmful in Rett syndrome



TSHA-102's novel miRNA-Responsive Auto-Regulatory Element (miRARE) technology is designed to correct *MECP2* deficiency and avoid toxic overexpression

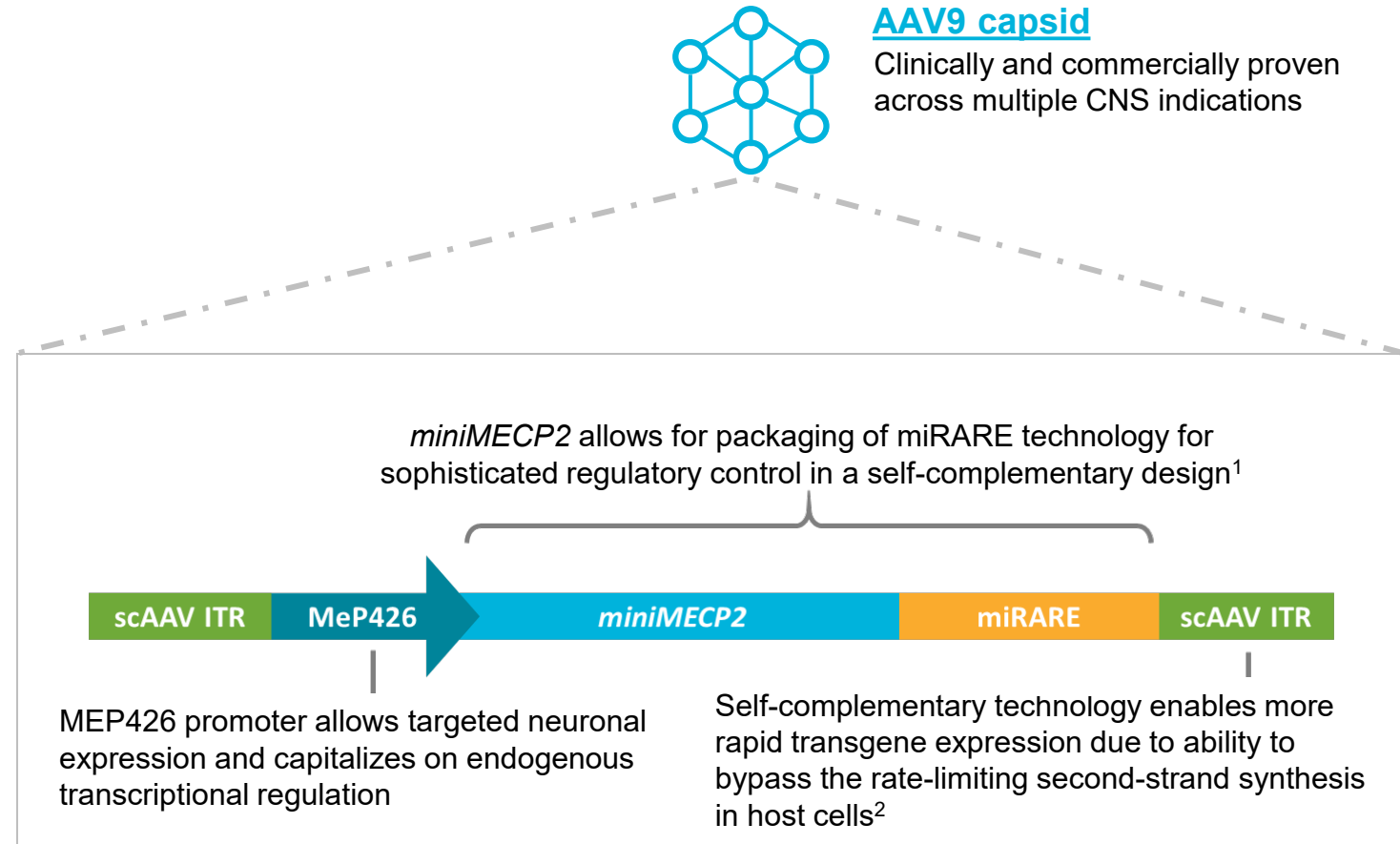
TSHA-102: an investigational one-time gene therapy that regulates *MECP2*

- TSHA-102 delivers a functional form of *MECP2* to cells in the CNS
- Equipped with novel miRNA-responsive target sequence (miRARE) designed to mediate levels of *MECP2* in the CNS on a cell-by-cell basis without risk of overexpression
 - Senses transgene and endogenous *MECP2* levels to provide a superior therapeutic profile to that of unregulated *MECP2* gene replacement³
- Delivered via intrathecal (IT) administration to target key CNS regions and minimize viral load using a routine, minimally invasive procedure in an outpatient setting



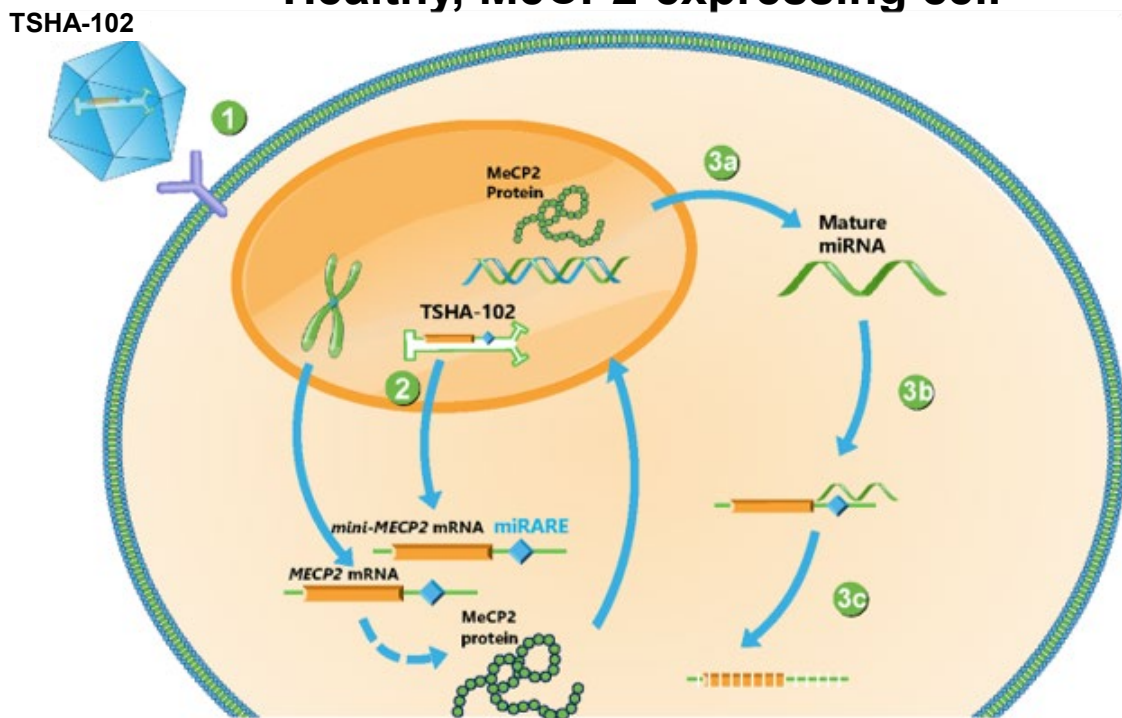
AAV9 capsid

Clinically and commercially proven across multiple CNS indications

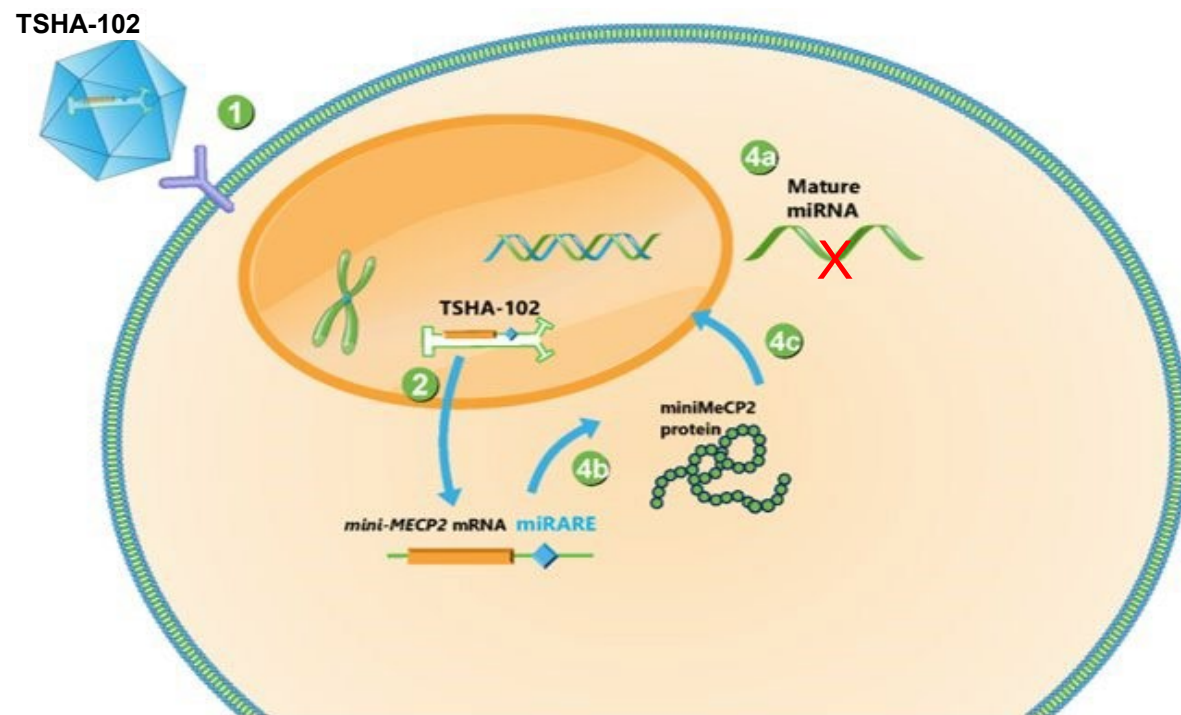


miRARE prevents overexpression through RNA interference with binding sites for endogenous microRNA responsive to MeCP2 levels¹

Healthy, MeCP2-expressing cell



MeCP2-deficient cell



Designed to silence the *miniMECP2* transgene in cells that already express MeCP2

Designed to enable miniMeCP2 protein production in MeCP2-deficient cells

TSHA-102 has demonstrated the ability to produce and maintain safe transgene expression levels in the CNS in preclinical models¹

Compelling preclinical safety, pharmacology, toxicology & biodistribution data supported clinical advancement of TSHA-102 in a broad age range of patients

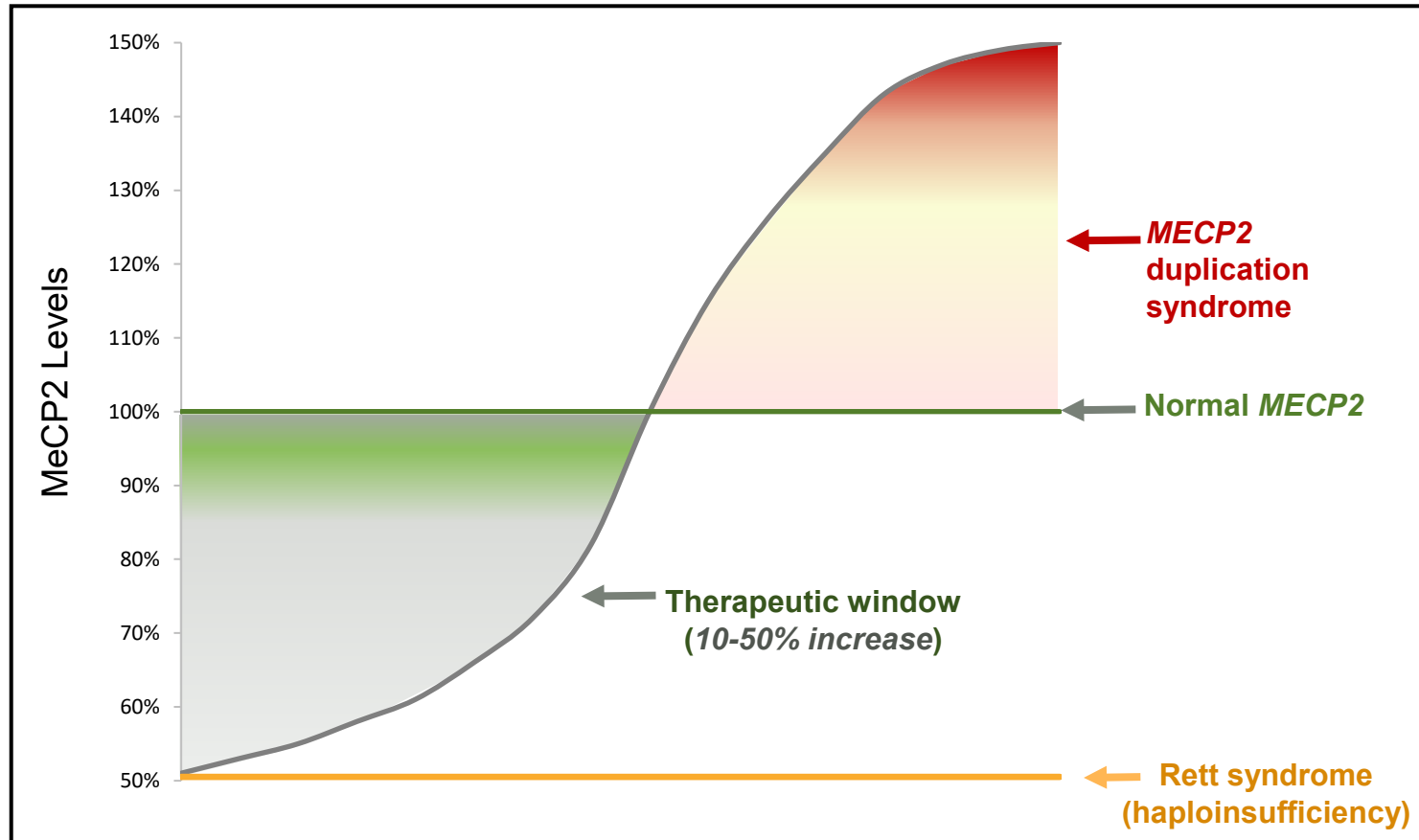
- TSHA-102 improved survival rate, overall neurobehavioral function and growth in neonatal KO Rett mice, with no impact on WT treated mice
- TSHA-102 demonstrated significant improvement in survival, body weight, motor function and respiratory health across all ages in KO Rett mice, with no impact on WT
- In 6-month GLP toxicology studies, single intrathecal administration of TSHA-102 up to 2.0×10^{15} vg/animal was well tolerated in WT rats and NHPs
- Broad biodistribution to brain and spinal cord demonstrated
- Vehicle and treated animals demonstrated similar levels of *MECP2*, supporting the mechanism of miRARE regulation
- miRARE downregulated *MECP2* transgene and protein expression in response to cellular levels of MeCP2 in human and mouse cell lines

Robust preclinical data for TSHA-102 across age ranges

Species	Animal Model	Age	Study Size	Purpose	HED (vg / participant)	Route of Administration	Findings
Mouse	Wild-type and <i>Mecp2</i> ^{-Y}	Neonates (P2)	n=45	Survival	2.9x10 ¹⁴	ICV	<ul style="list-style-type: none"> Improvement in survival rate, overall neurobehavioral function and growth in neonatal KO Rett mice No impact on WT treated mice
Mouse	Wild-type and <i>Mecp2</i> ^{-Y}	P7, P14, P28	n=252	Pharmacology	2.9x10 ¹⁴ 7.1x10 ¹⁴ 1.4 x 10 ¹⁵ 2.9x10 ¹⁵	IT	<ul style="list-style-type: none"> Significant improvement in survival, body weight, motor function and respiratory health across treatment ages No signs of overexpression in WT mice
Mouse	Wild-type and <i>Mecp2</i> ^{-Y}	P28 - P35	n=137	Biodistribution and gene expression	2.9x10 ¹⁵	IT	<ul style="list-style-type: none"> TSHA-102 vector DNA in liver and spinal cord (largest amount), brain and sciatic nerve (lowest amount) miniMECP2 RNA detected in brain and spinal cord
Rat	Wild-type	3.4 - 6.1 weeks	n=160	Toxicology	2.5x10 ¹⁴ 5.0x10 ¹⁴ 2.0x10 ¹⁵	IT	<ul style="list-style-type: none"> Favorable safety profile of TSHA-102 Nerve conduction metrics within functional physiological ranges for all groups at all timepoints Motor nerve conduction studies normal
NHP	Wild-type	Juvenile (~2 yrs)	n=24	Toxicology	2.5x10 ¹⁴ 5.0x10 ¹⁴ 2.0x10 ¹⁵	IT	<ul style="list-style-type: none"> TSHA-102 well tolerated with no toxicity observed Biodistribution to brain and spinal cord
Human and mouse cell lines	2v6.11, SH-SY5Y, and Neuro-2a	NA	NA	Gene and protein expression	NA	Cell transfection and transduction	<ul style="list-style-type: none"> Evidence that miRARE can control miniMECP2 transgene and protein expression in cell culture models miniMeCP2 protein expression induced by absence of cellular MeCP2

10% increase in MeCP2 protein in humans may be clinically significant based on mouse data¹

Some autonomic dysfunction may not resolve with 10% increase in MeCP2 protein



Phenotype Examples:

MECP2 duplication syndrome:

- Hypotonia from infancy
- Speech abnormalities
- Intellectual disability
- Seizures

Rett syndrome:

- Slowing and / or regression of development
- Loss of hand function, repetitive movements of hands
- Loss of communication abilities
- Difficulties with walking
- Breathing abnormalities
- Seizures

REVEAL Phase 1/2 adolescent and adult trial in U.S. and Canada

Open-label, dose-escalation and dose-expansion, randomized, multi-center trial for TSHA-102

Study Overview

Objectives

- Safety and preliminary efficacy of TSHA-102
- **Part A:** evaluates two dose levels (n=2 low dose, n=3 high dose); if possible, establishes MAD or MTD
- **Part B:** evaluates the MAD or MTD

Key inclusion criteria

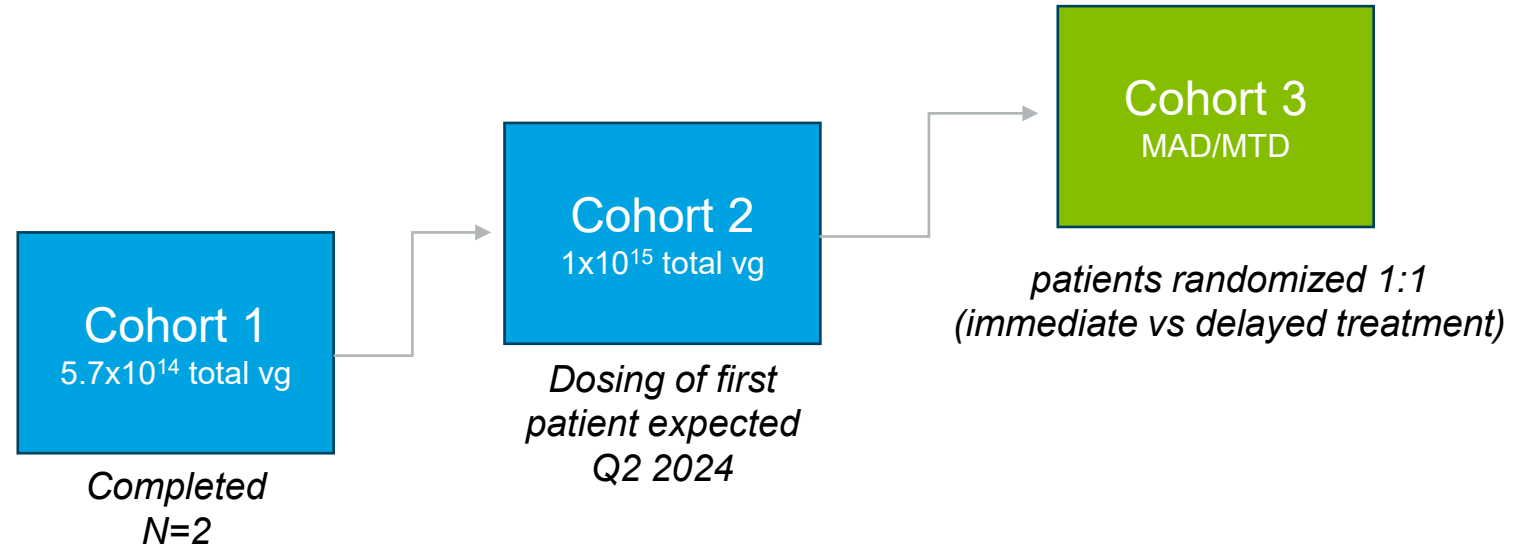
- Females aged 12+ with pathogenic confirmation of *MECP2* mutation
- CGI-S score of ≥ 4 at screening

Key clinical assessments

- Revised Motor Behavior Assessment Scale (R-MBA)
- Clinical Global Impression Scale-Severity and Improvement (CGI-S and CGI-I)
- Parental Global Impressions Scale-Improvement (PGI-I)
- Rett Syndrome Behavior Questionnaire (RSBQ)
- Rett Syndrome Hand Function Scale (RSHFS)

Part A: Dose Escalation

Part B: Dose Expansion



Initial cohort two data (high dose) expected 2H 2024

First two adult patients dosed had stage four Rett syndrome with different genetic mutation severity and phenotypic expression

Baseline Characteristics	
Patient One	Patient Two
<i>Diagnosed with stage four “late motor deterioration muscle wasting” Rett syndrome</i>	
20 year-old female	21 year-old female
Large <i>MECP2</i> deletion	Missense <i>MECP2</i> mutation
Severe phenotype	Milder phenotype
“Severely ill” – CGI-S baseline score of 6	“Moderately ill” – CGI-S baseline score of 4
Complete loss of ambulation Wheelchair-bound Loss of hand function Mostly non-verbal Frequent apnea, hyperventilation and seizures	Partial loss of ambulation Walks with impaired gait and balance Hand stereotypies with weak grasping Mostly non-verbal Frequent hyperventilation and seizures

TSHA-102: encouraging safety profiles and consistent clinical improvement observed in first two adult patients dosed in cohort one (low dose)

Generally well-tolerated

No treatment-emergent SAEs as of week 35 assessment (patient one) and week 19 assessment (patient two)

Improvements across key efficacy measures

Sustained and new improvement at decreased steroid levels at month six (patient one) and sustained and new improvement at week 12 (patient two)

Improvements across multiple clinical domains

Principal Investigator observed sustained and new improvements across multiple domains including autonomic function, socialization/communication, motor skills, and seizures, following completion of steroid taper at week 35 (patient one) and at decreased steroid levels at week 19 (patient two)

Continued improvements observed across multiple clinical domains and efficacy measures in both adult stage four patients with different genetic mutation severity and phenotypic expression

Sustained and new improvement seen across multiple clinical domains in both adult patients based on clinical observations from Principal Investigator

Clinical Domain	Patient One 35-weeks post-treatment	Patient Two 19-weeks post-treatment
Autonomic function	Improved breathing patterns, sleep quality/duration and circulation	Improved breathing patterns and circulation
Socialization / Communication	Improved social interest, vocalization, and use of eye-driven communication device	Improved social interest
Motor skill	Improved hand function and gained ability to sit unassisted and move legs for the first time in over a decade	Improved hand stereotypies
Seizures	Stable seizure events with lower levels of anti-seizure medication relative to baseline	Significantly reduced seizure events with lower levels of anti-seizure medication relative to baseline
Overall change	+	+

Clinical improvement demonstrated across key efficacy measures in patient one (six-month data) and patient two (12-week data)

Scale Description	CGI-S		CGI-I, with Rett anchors		PGI-I		RSBQ		R-MBA		RSHFS	
	P1	P2	P1	P2	P1	P2	P1	P2	P1	P2	P1	P2
<p>Clinician-reported 7-point assessment of illness severity 1=<i>normal</i> 7=<i>among the most extremely ill</i></p> <p>Clinician-reported 7-point assessment of overall improvement 1=<i>very much improved</i> 7=<i>very much worse</i></p> <p>Caregiver-reported 7-point assessment of overall improvement 1=<i>very much improved</i> 7=<i>very much worse</i></p> <p>Caregiver-reported 45-item questionnaire to assess Rett syndrome characteristics <i>Higher scores indicate greater severity</i></p> <p>Clinician-reported 24-question scale measuring disease behaviors of Rett syndrome <i>Higher scores indicate greater severity</i></p> <p>Clinician-reported assessment of hand function in Rett syndrome by an independent experienced physical therapist, being reported as best score for large objects 1=<i>no active grasping</i> 4=<i>independent grasp</i></p>												
Screening, Baseline	6 Severely ill	4 Moderately ill	–	–	–	–	52	37	43	38	DH: 3 NH: NA*	DH: NE* NH: 1
Week 4	5 Markedly ill	4 Moderately ill	2 Much improved	3 Minimally improved	3 A little better	3 A little better	29	33	48	31	NA*	DH: NE* NH: 1
Week 8	5 Markedly ill	4 Moderately ill	2 Much improved	3 Minimally improved	3 A little better	3 A little better	27	33	51	24	DH: 2 NH: 1	DH: 4 NH: 1
Week 12	5 Markedly ill	4 Moderately ill	2 Much improved	3 Minimally improved	2 Much better*	3 A little better	30	35	37	21	DH: 3 NH: 3*	DH: NE* NH: 1
Week 25	5 Markedly ill	–	2 Much improved	–	2 Much better	–	22	–	42	–	DH: 3 NH: 2	–
Overall Change	+	=	+	+	+	+	+	+	+	+	+	=

DH=dominant hand; NH=non-dominant hand; NA=not assessed; NE=not evaluable; + indicates improvement from baseline; = indicates no change from baseline

*PGI-I week 12 assessment was captured at week 16; RSHFS for patient one's NH was not assessed at baseline; RSHFS for patient one was not assessed at week 4; RSHFS week 12 assessment for patient one was captured on week 11; RSHFS assessment for patient two's DH was not conducted as defined in the guidelines at baseline, week 4 and week 12, therefore the data is not evaluable at these time points.

REVEAL Phase 1/2 pediatric trial in the U.S. and U.K.

Open-label, dose-escalation and dose-expansion, randomized, multi-center trial for TSHA-102

Study Overview

Objectives

- Safety and preliminary efficacy of TSHA-102
- **Part A:** evaluates two dose levels (n=3 per dose); if possible, establishes the MAD or MTD
- **Part B:** evaluates the MAD or MTD in two age cohorts

Key inclusion criteria

- Females 5-8 years old with pathogenic confirmation of *MECP2* mutation (Part A)

Key clinical assessments

- R-MBA
- CGI-S and CGI-I
- PGI-I
- RSBQ
- Adapted Mullen Scales for Early Learning (MSEL-A)

Part A: Dose Escalation

Cohort 1
5.7x10¹⁴ total vg
5-8 years old

Dosing of second patient expected Q1 2024

Cohort 2
1x10¹⁵ total vg
5-8 years old

Part B: Dose Expansion

Cohort 3
MAD/MTD
5-8 years old

Cohort 4
MAD/MTD
3-5 years old

patients randomized 1:1 (immediate vs delayed treatment)

Initial data for cohort one (low dose) expected in mid-2024, and for cohort two (high dose) in 2H 2024

Anticipated TSHA-102 2024 program milestones

Q1 2024	Dose second patient in cohort one (low dose, n=3) of 5.7×10^{14} total vg in REVEAL Phase 1/2 pediatric trial
Q2 2024	Dose first patient in cohort two (high dose, n=3) of 1×10^{15} total vg in REVEAL Phase 1/2 adolescent and adult trial
Mid-2024	Report initial safety and efficacy data from cohort one (low dose) of 5.7×10^{14} total vg in REVEAL Phase 1/2 pediatric trial
H2 2024	Report initial safety and efficacy data from cohort two (high dose) of 1×10^{15} in both REVEAL trials

Financial Position

- Cash balance of \$143.9 million as of December 31, 2023
- Cash runway expected to fund operating expenses and capital requirements into 2026 through key TSHA-102 inflection points

TSHA-102 – *a differentiated approach to treat all patients with Rett syndrome*

Designed to safely address the root cause of Rett syndrome in an outpatient setting

Encouraging initial Phase 1/2 data in adults with most advanced stage of disease

Well-capitalized through key inflection points