

## **Corporate Presentation**

May 2024

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Neurogene is a Differentiated Clinical-Stage Company Utilizing EXACT™ Technology to Treat Complex Neurological Diseases



## Neurogene Clinical Stage Pipeline



\*IND = investigational new drug.



Multiple discovery stage assets in development with plans to advance one program into the clinic in 2025

### EXACT Developed to Solve the Limitations of Conventional Gene Therapy in Complex Neurological Disorders

Today's Gene Therapy is Limited By:		Neurogene's Solutions:		
	Variable Gene Expression	~	Novel, modular EXACT gene regulation technology and other regulatory elements designed to optimize transgene expression to maximize the therapeutic window	
	Safety Limitations	~	Novel and proprietary EXACT gene regulation technology designed to avoid transgene related toxicity associated with conventional gene therapy	
	Inefficient Gene Delivery	~	Select ICV delivery approach to maximize AAV9 distribution to target CNS tissues	
V				

= intracerebroventricular ( = adeno-associated virus

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## Wholly-Owned and Fully Integrated In-House AAV Manufacturing



- Flexibility to manufacture AAV product at low cost
- Own product quality and development timelines

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ENE

- Process development expertise supports both HEK293 and Sf9/rBV manufacturing platforms
- Flexibility to rapidly adapt CMC execution to program needs

Current research and clinical-grade manufacturing capabilities are designed for commercial-grade product to avoid potential future comparability challenges



## Experienced Leadership Team

### **Management Team**

Rachel McMinn, Ph.D. Founder and CEO

Intercept

Bank of America 🤎 Merrill Lynch



GENE THERAPIES Lilly Dendreon (NPS Pharma. Miclone Systems Incorporated

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Amicus FDA U.S. FOOD & DRUG

Johnson »Johnson

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AUSPEX





## **NGN-401 for Rett Syndrome**

Leveraging EXACT gene regulation technology

## Rett Syndrome – Devastating Disorder with High Unmet Need





### **Genetics**

- X-Linked disorder causing mutations in the gene encoding for methyl-CpG binding protein 2 (MeCP2)
- Unknown incidence in boys, but typically lethal by ~3 years of age due to no healthy copy of MeCP2



### **Compelling Market Opportunity**

- U.S. prevalence ~6,000-9,000 patients
- WW incidence 1:10,000-1:15,000 live female births



### **High Unmet Need**

- There are no approved treatments that address root cause of disease
- Significant unmet need remains for new treatment options



U.S. prevalence estimate based on published incidence rates; Laurvick CL, et al. J Pediatr 2006;148(3):347–35. WW incidence estimate based on published incidence rates; Pini G, et al. Orphanet Journal of Rare Diseases (2016) 11:132.

## Rett Syndrome Treatment Requires Tight Gene Regulation



- Rett syndrome (RTT) is a severe neurological disorder caused by mosaic mutations in X-linked MeCP2 gene
- Mice modeling RTT recapitulate many neurological phenotypes observed clinically; disease reversibility has been demonstrated in both immature and mature adult animals

NGN-401 is designed to deliver therapeutic levels of MeCP2 to deficient cells while maintaining a non-toxic level in unaffected cells

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## EXACT Acts As a Genetic Thermostat, Limiting Transgene Expression

EXACT miRNA controls transgene levels to targeted range

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Regulatory elements designed to avoid offtarget effects



EXACT is expected to enable gene therapy for Rett syndrome and other complex disorders





## EXACT Designed to Widen Therapeutic Window and Enable Gene Therapy for Rett Syndrome





•~50% of cells express WT levels of MeCP2

0~50% are MeCP2 deficient



NGN-401 Demonstrates Efficacy and Safety in Mecp2 Mouse Models



ICV Delivery of NGN-401 Delivers Targeted MeCP2 Levels

← Male or female + Vehicle

ENE Het=heterozygous for Mecp2, mirroring genetic makeup of human females with Rett syndrome

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## ICV Administration Significantly Better Distribution Than IT-L To Key Areas of the Nervous System Underlying Rett Syndrome in NHPs



## NGN-401 Preclinical Data Enabled Pediatric Clinical Approach



U.S. FDA, UK MHRA and Australian HREC cleared dosing directly into pediatric patients

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## Cardinal Clinical Features of Rett Syndrome

### Inability to Communicate

- Loss of purposeful hand use & involuntary hand movements
- Loss of spoken language

### Impaired Fine and Gross Motor Skills

- Loss of hand function
- Gait abnormalities
- Ambulation requiring assistance or non-ambulatory

### Autonomic Dysfunction

- Severe apnea episodes
- Hyperventilation
- Constipation
- Difficulty swallowing
- Sleep disturbance

### Additional Disease Manifestations

- Seizures
- Anxiety
- Scoliosis
- Muscle contractures

Normal Developr Regression



Birth

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 $\sim$ 1-4 vrs

G, et al. Orphanet Journal of Rare Diseases (2016) 11:132.

"Relative" stability Risk of scoliosis increases Risk of seizures developing Hand function loss



GI tube placement common Spinal fusion surgery common Significant muscle rigidity/contractures Increased mobility loss



# Phase 1/2 Trial for NGN-401 Designed to Inform Future Pivotal Clinical Trial



- Cohort 1 dose of 1E15 vg (total), Cohort 2 dose of 3E15 vg (total)
- Cohorts to enroll concurrently
- Both doses within GLP toxicology safety margin
- Key assessments at 3, 6, 9 and 12 months, which include caregiver and clinician assessments RSBQ, CGI-I and CGI-S

### **Key Eligibility Criteria**

- Female, age ≥4 to ≤10 years with Classic Rett syndrome
- Clinical diagnosis & genetic confirmation of pathogenic MeCP2 mutation
- Clinical Global Impression-Severity (CGI-S) score of 4-6

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#### **Efficacy Assessments of Interest**

Autonomic Function	Objective device to monitor breathing	
Hand Function	Physician assessment of improvement	
Communication	Physician assessment of improvement	
Gross Motor Function	Physician assessment of improvement	

## NGN-401 Study Inclusion Criteria is Driven by Severity of Rett Syndrome Domains Under CGI-S

	Limited	impairment	Modest impairment	Eligible fo	or Phase 1/2	clinical trial	
Clinical domains	CGI-S=1	CGI-S=2	CGI-S=3	CGI-S=4	CGI-S=5	CGI-S=6	CGI-S=7
Language/ Communication	Normal	May have unusual features (eg echolalia, reading disability)	Phrases-sentences. May have conversations or echolalia	<5 words Babbles Makes choices 25%- 50%	No words Babbles Makes choices ≤25%	Vocalizations Occasionally screams Rarely or makes no choices	No words No vocalizations Screams No choices
Ambulation	No impairment	Normal, may have slight evidence of dystonia/ ataxia/ dyspraxia	Walks, able to use stairs/run May ride tricycle or climb	Walks independently Unable to use stairs or run	Walks with assistance	Stands with support or independently May walk with support Sits independently or with support	Cannot sit Doesn't stand or walk
Hand use	Normal, no impairment	Normal, may have slight fine motor issue	Bilateral pincer grasp. May use pen to write but has fine motor issues like tremor	Reaches for objects, raking grasp or unilateral pincer May use utensils/cup	Reaches No grasps	Rarely-occasionally reaches out No grasp	None
Social (eye contact)	Normal	Occasional eye gaze avoidance	Appropriate eye contact, >30s	Eye contact <20s	Eye contact <10s	Eye contact, inconsistent 5s	None
Autonomic	None	Minimal	No or minimal breathing abnormalities (<5%) warm, pink extremities	Breathing dysrhythmia <50% No cynanosis Cool UE, Pink LE	Breathing dysrhythmia 50% No cynanosis Cold UE, Pink LE	Breathing dysrhythmia 50-100% May have cynanosis Cool UE or LE, may be blue	Breathing dysrhythmia constantly with cynanosis Cold UE and LE, Mottled/blue
Seizures	None	None or controlled	None, with or without meds	Monthly-weekly	Weekly	Weekly-daily	Daily
Attentiveness	Normal	Occasional inattention	Attentive to conversation, follows commands	50-100%	50%	<50%	0%

## NGN-401 Has Been Generally Well-Tolerated in First Three Patients Dosed in Cohort 1

### **Baseline Demographics**

	Patient 1	Patient 2	Patient 3
Age at Dosing	7 years old	4 years old	6 years old
Race	Asian	White	White
MECP2 mutation	Mild	Severe	Severe
Time post- NGN- 401 administration	~9 months	~6 months	~3 months

- All treatment-emergent adverse events (TEAEs) related to NGN-401 have been mild/Grade 1 and transient or resolving, and most AEs are known potential risks of AAV
- There have been no treatment-emergent or ICV procedure-related serious AEs (SAEs)
- No signs or symptoms indicative of MeCP2 overexpression toxicity have been reported in any participant, including Patient 1 who has a mild variant predicted to result in residual MeCP2 expression



# NGN-401 Phase 1/2 Clinical Trial Status Update and Anticipated Milestones

### Phase 1/2 Clinical Trial Status

- First patient dosed 3Q:23, second patient dosed 4Q:23, third patient dosed 1Q:24
- No treatment-emergent, procedure-related serious adverse events or overexpression toxicity observed to date

### 2024 Anticipated Key Milestones

- Expand ongoing Phase 1/2 clinical trial in 1H:24 to enroll a larger cohort of patients
- □ Initiate dosing of Cohort 2 in 2Q:24
- Complete dosing of Cohort 1 in 2H:24
- Interim Phase 1/2 clinical data 4Q:24
- Additional Phase 1/2 clinical data from expanded low dose and high dose cohorts in 2H:25

## NGN-101 for CLN5 Batten Disease

Treating both CNS and vision through dual route of administration

# CLN5 Batten Disease - Fatal, Neurodegenerative Disease With No Disease-Specific Treatment Options

## CLN5 Batten disease has no available treatment options

Brineura, approved globally for a similar indication, CLN2, has transformed clinical outcomes in Batten disease

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G E N E Simonati A et al, Phenotype and natural history of variant late infantile ceroid-lipofuscinosis 5. Dev Med Child Neurol. 2017 Aug;59(8):815-821.

## NGN-101 Dual Delivery Supported by Compelling Preclinical Data

Dual route of administration

First clinical gene therapy study targeting both neurodegeneration and vision loss



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IVT = Intravitreal

### NGN-101 dosing (ICV+IVT) in CLN5 knockout sheep

Combination dosing leads to halting of disease progression



## Clinical Study Design For NGN-101 Addresses Vision and CNS



#### Dose selection based on sheep studies showing significant treatment effects

• Key assessments every 6 and 12 months

### Key Eligibility Criteria

- Age  $\geq$ 3 to  $\leq$ 9 years
- Genetic diagnosis of CLN5
- Onset of disease ≤5 years of age
- Score of ≥1 on the Hamburg motor domain at minimum, the equivalent of 20/200 visual acuity or better at the time of screening

### Efficacy Endpoints/Markers of Interest

Optical Coherence Tomography (OCT)	Preservation of key retinal layers is a leading indicator of vision stability	
Visual Acuity	Stability in treated eye vs. worsening in untreated eye could provide evidence of clinical benefit	
Hamburg Motor Scale	Scale has been used previously to support BMRN's ERT Brineura® for CLN2 disease	

## NGN-101 — Defining a Registration Path

### FDA meeting focused on finalizing CMC plans completed 4Q:23



### **Potency Assay**

FDA accepted proposed potency assay strategy, a first milestone in determining continuation of the program



### Improved Manufacturing Process

FDA alignment on proposed comparability strategy for using Neurogene-made material with substantially improved profile to Phase 1/2 drug product

## Plan to request FDA meeting in 2H:24 to align on clinical requirements for streamlined registration



Complete enrollment of high dose cohort in 2024



Continue collection of clinical trial data on vision and motor for analysis



Ongoing natural history data analysis

### Alignment with FDA on streamlined registration pathway required to move program forward





## Key Anticipated Milestone Events

### Key Upcoming Anticipated Milestones and Pipeline Developments

### Rett syndrome (NGN-401)

- Expand ongoing Phase 1/2 clinical trial in 1H:24 to enroll a larger cohort of patients
- Interim Phase 1/2 clinical data 4Q:24
- Additional Phase 1/2 clinical data from expanded low dose and high dose cohorts in 2H:25

### CLN5 Batten disease (NGN-101)

- Interim Phase 1/2 clinical data in 2H:24
- Engage in FDA discussions regarding a streamlined registrational pathway in 2H:24

### Early-stage discovery

Advance one program into the clinic (2025)

Approximately \$170 million cash on hand as of March 31, 2024, expected to fund operations into 2H:26



## Why Neurogene?







# Appendix

# Rett Syndrome Primarily Results from Loss of *MECP2* Function in the Brain, Making the Brain the Key Target Area for Gene Therapy



- Limiting expression of MeCP2 to only the brain/spinal cord results in a near normal mouse
- NHP biodistribution study shows 10-100x greater distribution for ICV/ICM compared to IT-L

 Delivery of NGN-401 via ICV chosen to maximize *MECP2* expression in the brain

## EXACT Delivers Consistent Levels of *MECP2* Expression on Cellby-Cell Basis



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ENE

NGN-401 Demonstrates Tight *MECP2* Regulation That Translates to Compelling Outcomes in a Knockout Mouse Model



### ICV Delivery of NGN-401 Delivers Targeted MeCP2 Levels

NEUROGENE \*RTT scored 0-5 for six domains: mobility, gait, clasping, breathing, tremor, body condition

## NGN-401 Via ICV Delivery Well Tolerated in Multiple Studies While Conventional Unregulated Gene Therapy is Toxic



ENE \*Regulated includes NGN-401 and another EXACT vector; data at 30 days

NCV=nerve conduction velocity; NHP = non-human primates

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## NGN-401 Distribution and Expression Levels in NHPs Support Encouraging Profile for Human Testing

- NGN-401 distributes to key regions underlying RTT pathophysiology in WT non-human primates
- Degree of mRNA expression tracks vector genome biodistribution of AAV9 across key brain regions
- Aggregate transgene expression below levels of endogenous MECP2 mRNA (100% of cells), avoiding
  overexpression concerns

Vector Biodistribution with ICV Administration Addresses Key Areas of the Brain Affected in Rett Syndrome





## GLP Toxicology in NHPs Support Favorable Safety Profile

- NGN-401 evaluated in GLP NHP toxicology study with 90-day and 180-day cohorts
- No signs or symptoms of MeCP2 overexpression observed
- >4x safety margin relative to NGN-401 clinical starting dose in Phase 1/2
- Overall toxicology profile consistent with typical profile of intra-CSF administered AAV9 product
  - Slight to minimal non-adverse pathology detected in the dorsal root ganglion (DRG) nerves
  - Early and transient liver enzyme elevations observed, which resolved quickly without intervention



## Explanation of CGI-I and RSBQ

### CGI-I (Clinician Global Impression of Improvement)



### RSBQ (Rett Syndrome Behavior Questionnaire)

Score	Definition
0	not true
1	somewhat or sometimes true
2	very true

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Domain	Total Possible Points (90)
General mood	16
Breathing problems	10
Hand behaviors	12
Repetitive face movements	8
Body rocking and expressionless face	12
Nighttime behaviors	6
Fear/anxiety	8
Walking/standing	4
Other	14