Neurogene Announces Registrational Trial Design for Embolden™ Study of NGN-401 Gene Therapy for Rett Syndrome

June 30, 2025

Written agreement from FDA for single-arm, open-label, baseline-controlled registrational trial evaluating composite primary endpoint of improvement in CGI-I and gain of developmental milestone/skill by video capture

Written agreement from FDA to evaluate NGN-401 in females with Rett syndrome ages 3 years and older based on natural history study analysis

Registrational trial initiation activities underway

Phase 1/2 trial fully enrolled, with 5 participants dosed in 1H 2025, showing no evidence of HLH/hyperinflammatory syndrome at 1E15 vg dose

Cash runway extended into early 2028

NEW YORK--(BUSINESS WIRE)--Jun. 30, 2025-- Neurogene Inc. (Nasdaq: NGNE), a clinical-stage company founded to bring life-changing genetic medicines to patients and families affected by rare neurological diseases, today announced details of Embolden™, the Company's registrational clinical trial designed to evaluate NGN-401 gene therapy for the treatment of females with Rett syndrome in participants ages 3 years and older. The Company has written agreement from the U.S. Food and Drug Administration (FDA) on key aspects of the registrational trial's design.

"We appreciate the partnership with the FDA as we aligned on the key elements of our NGN-401 registrational trial design, which will allow for rapid conversion of the current Phase 1/2 study to a pivotal trial," said Rachel McMinn, Ph.D., Founder and Chief Executive Officer of Neurogene. "We believe that the robust endpoint design, which was informed by key opinion leaders, caregiver input and primary market research with payors, will support NGN-401's best-in-class potential and provide key differentiating data critical to the Rett syndrome community and the future commercial success of NGN-401."

"I appreciate the multi-domain approach across the clinical manifestations of Rett syndrome, and rigor in which the primary endpoint will be evaluated, including both the clinician perspective of improvement using the CGI-I scale with Rett syndrome anchors and videos to demonstrate gains of skills that are clinically meaningful for girls and women with Rett syndrome and their families," said Elizabeth M. Berry-Kravis, M.D., Ph.D., Professor of Pediatrics, Neurological Sciences and Biochemistry at Rush University, and principal investigator in the NGN-401 clinical trial. "Participants treated with NGN-401 have demonstrated increased independence, with both fine and gross motor function improvement, and gained the ability to better communicate wants, needs and choices. I have been impressed with the improvements observed in participants after NGN-401 administration, which have included global improvement in signs and symptoms of Rett syndrome and gains of multi-domain developmental milestones that would not be expected to occur spontaneously in the post-regression stage of Rett syndrome. Evaluating treatment effect in participants ages 3 and above in the registrational study will provide important insights on the potential benefits of NGN-401 in younger patients early in the course of this progressive disease."

Obtained Written Agreement from FDA on the Following Key Elements of Embolden Registrational Trial Design After Discussions Under the START Program

- **Study Design:** Open-label, single arm, baseline control (i.e., participants serving as their own control); N=18 proposed, subject to feedback from the FDA.
- **Patient Population**: Females ages ≥ 3 years with Rett syndrome, which is consistent with Neurogene's analysis of the NIH-sponsored, International Rett Syndrome Foundation (IRSF) Rett syndrome natural history study that shows patients ages 3 and above rarely learn new skills/reach developmental milestones or relearn skills once lost. The FDA's written agreement endorsed the Company's analysis.
- **Dose**: 1E15 vector genomes (vg).
- **Primary Endpoint:** Responder-based composite endpoint that will assess an improvement in the Clinical Global Impression-Improvement (CGI-I) scale with Rett syndrome anchors and the gain of a developmental milestone/skill, compared to a participant's own baseline. Responders are defined as participants who:
    - Attain a CGI-I score of ≤ 3 ("minimally improved"); and
    - Gain any one developmental milestone/skill from a list of 28, as captured through standardized video recordings and independently verified by blinded central raters.
        - Developmental milestones/skills were informed by a Rett syndrome caregiver survey, provided to the FDA, demonstrating that the acquisition of any single skill within the selected set is considered clinically meaningful.
    - The primary endpoint will be evaluated at 12 months following NGN-401 administration, with feedback pending from the FDA to consider the addition of a 6-month endpoint.

Neurogene has begun registrational trial initiation activities.

"It has been incredibly rewarding to see how RSRT's early investments in foundational Rett syndrome science helped lay the groundwork for what's now a promising gene therapy program approaching a registrational trial," said Monica Coenraads, Founder and Chief Executive Officer of RSRT. "RSRT has been a long-time champion of addressing the underlying genetic cause of Rett syndrome and Neurogene's program has the potential to do just that. We appreciate the thoughtful design of the trial that importantly incorporates the caregiver perspective on what meaningful improvement may

look like. We congratulate the Neurogene team on reaching alignment with the FDA and thank the Rett community at large for their support in advancing this program. The future is bright!"

"Our partnership with Neurogene reflects a shared commitment to accelerating meaningful treatments for Rett syndrome," said Laura Hameed, Chief Executive Officer of the International Rett Syndrome Foundation (IRSF). "The use of IRSF's Natural History Study data to support the NGN-401 gene therapy registrational trial design is a powerful example of how families accelerate and streamline therapeutic development. We are grateful to the families that contributed to the NHS, and to the families participating in this trial whose time and commitment are essential to evaluating gene therapy for Rett syndrome."

Phase 1/2 Trial Data Support Registrational Trial Design

Previously disclosed clinical data from the Phase 1/2 study* support the registrational trial design. Data showed improvements in Rett syndrome assessments with an aggregate of 23 developmental milestones/skills acquired in the first four participants. Specifically, the four participants:

- Each achieved a clinically meaningful rating of 2, or "much improved," on the CGI-I; and
- Collectively achieved 23 developmental milestones/skills in the core clinical domains of Rett syndrome – hand function/fine motor, communication/language, and ambulation/gross motor, including:
    - Participant 1 gained 10 skills across multiple domains by 15 months post-dose;
    - Participant 2 gained 8 skills across multiple domains by 12 months post-dose;
    - Participant 3 gained 3 skills across multiple domains by 9 months post-dose; and
    - Participant 4 gained 2 skills by 3 months post-dose.

*Efficacy data from the first four participants; as of data cut-off date of October 17, 2024

Phase 1/2 Trial Enrollment and Update

Neurogene previously shared that five additional participants had been dosed in the Phase 1/2 portion of the NGN-401 clinical trial during the first half of 2025. A total of 10 participants have received the 1E15 vg dose. There has been no evidence of hemophagocytic lymphohistiocytosis (HLH) / hyperinflammatory syndrome in any participant at the 1E15 vg dose level. Neurogene remains on track to share updated clinical efficacy and safety data in the second half of 2025.

Cash Runway Update

As of March 31, 2025, Neurogene had cash, cash equivalents, and investments of $292.6 million. The Company's current budget reflects a reallocation of capital from pipeline development to support pivotal trial activities for NGN-401. Neurogene now expects its existing resources will be sufficient to fund operations into early 2028.

About Neurogene

The mission of Neurogene is to treat devastating neurological diseases to improve the lives of patients and families impacted by these rare diseases. Neurogene is developing novel approaches and treatments to address the limitations of conventional gene therapy in central nervous system disorders. This includes selecting a delivery approach to maximize distribution to target tissues and designing products to maximize potency and purity for an optimized efficacy and safety profile. The Company's novel and proprietary EXACT™ transgene regulation platform technology allows for the delivery of therapeutic levels while limiting transgene toxicity associated with conventional gene therapy. Neurogene has constructed a state-of-the-art gene therapy manufacturing facility in Houston, Texas. CGMP production of NGN-401 was conducted in this facility and will support pivotal clinical development activities. For more information, visit www.neurogene.com.

About NGN-401

NGN-401 is an investigational AAV9 gene therapy being developed as a one-time treatment for Rett syndrome. It is the first clinical candidate to deliver the full-length human *MECP2* gene under the control of Neurogene's EXACT™ transgene regulation technology. EXACT technology is an important advancement in gene therapy for Rett syndrome, specifically because the disorder requires a treatment approach that enables targeted levels of *MECP2* transgene expression without causing overexpression-related toxic effects associated with conventional gene therapy.

NGN-401 was selected by the U.S. Food and Drug Administration (FDA) for its START Pilot Program and has also received Regenerative Medicine Advance Therapy (RMAT) designation, orphan drug designation, Fast Track designation and rare pediatric designation from the FDA. Neurogene was previously granted an INTERACT meeting with the FDA regarding the EXACT technology. NGN-401 also received Priority Medicines (PRIME) designation, orphan designation and advanced therapy medicinal product designation from the European Medicines Agency (EMA) and the Innovative Licensing and Application Pathway (ILAP) designation from the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA).

Cautionary Note Regarding Forward-Looking Statements

Statements in this press release which are not historical in nature are intended to be, and hereby are identified as, forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These statements may discuss goals, intentions and expectations as to future plans, trends, events, results of operations or financial condition, or otherwise, based on current expectations and beliefs of the management of Neurogene, as well as assumptions made by, and information currently available to, management of Neurogene, including, but not limited to, statements regarding: trial designs, clinical development plans and timing for NGN-401, including elements of the registrational clinical study trial design subject to final approval of the FDA, such as the proposed number of participants in the Embolden trial and the addition of a six month endpoint, and timing of the conversion of the NGN-401 Phase 1/2 clinical trial to a registrational clinical trial; expected future interactions with or positions of the FDA; the safety, tolerability and efficacy of NGN-401; the potential for success of the Embolden registrational clinical trial for NGN-401 for the treatment of Rett syndrome; expected timing for additional interim data from the Company's NGN-401 Phase 1/2 trial for Rett Syndrome; the effectiveness of the monitoring and treatment protocol for HLH in Neurogene's Phase 1/2 clinical trial of NGN-401; and the time period over which existing cash resources may be sufficient to fund the Company's operations. Forward-looking statements generally include statements that are predictive in nature and depend upon or refer to future events or conditions, and include words such as "may," "will," "should," "would," "expect," "anticipate," "plan," "likely," "believe," "estimate," "project," "intend," "on track," and other similar expressions or the negative or plural of these words, or other similar expressions that are predictions or indicate future events or prospects, although not all forward-looking statements contain these words. Forward-looking statements are based on current beliefs and assumptions that are subject to risks, uncertainties and assumptions that are difficult to predict with regard to timing, extent, likelihood, and degree of occurrence, which could cause actual results to differ materially from anticipated results and many of which are outside of Neurogene's control. Such risks, uncertainties and assumptions include, among other things, uncertainties regarding

interactions with and feedback received from the FDA staff responsible for approving the design of our registrational trial and the risks and uncertainties identified under the heading "Risk Factors" included in Neurogene's Annual Report on Form 10-K for the year ended December 31, 2024, filed with the Securities and Exchange Commission (SEC) on March 24, 2025, Neurogene's Quarterly Report on Form 10-Q for the quarter ended March 31, 2025, filed with the SEC on May 9, 2025, and other filings that the Company has made and may make with the SEC in the future. Nothing in this communication should be regarded as a representation by any person that the forward-looking statements set forth herein will be achieved or that the contemplated results of any such forward-looking statements will be achieved. Forward-looking statements in this communication speak only as of the day they are made and are qualified in their entirety by reference to the cautionary statements herein. Except as required by applicable law, Neurogene undertakes no obligation to revise or update any forward-looking statement, or to make any other forward-looking statements, whether as a result of new information, future events or otherwise.

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