Gene Therapy Targeting CNS Diseases: ICV Administration as a Growing Standard for Delivery

Demystifying ICV Delivery in CNS Gene Therapy

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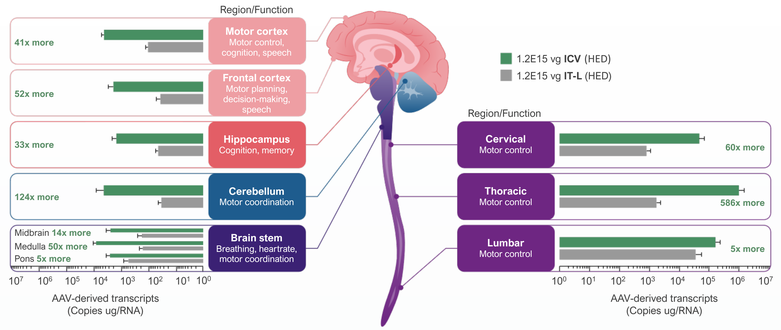
INTRODUCTION

- Adeno-associated virus (AAV)-based gene therapies for central nervous system (CNS) disorders are designed to deliver therapeutic transgenes to affected brain regions, with the goal of maximizing the potential for durable benefit by bypassing the blood-brain barrier with a single administration.[1–5]
- Multiple intra-cerebrospinal fluid (CSF) routes of administration (ROA), such as intrathecal lumbar (IT-L), intra-cisterna magna (ICM), and intracerebroventricular (ICV), have been applied to meet defined therapeutic biodistribution goals across a range of neurodegenerative and neurodevelopmental disorders.[1,2,6]
- Among these approaches, ICV ROA is a well established, routinely performed neurosurgical procedure, commonly used for shunt placement, enzyme replacement, chemotherapy delivery, and diagnostic access and is utilized by pediatric and adult neurosurgeons tens of thousands of times annually.[2,3]
- ICV ROA has been adopted by multiple mid- and late-stage clinical gene therapy programs, including those targeting Canavan disease, mucopolysaccharidosis type II (MPS II), Dravet syndrome, *SHANK3* haploinsufficiency, NGly1 deficiency, and Rett syndrome.[2]
- Importantly, clinical safety considerations for CNS gene therapies are driven primarily by the transgene expression, dose, and total viral load of the gene therapy product rather than the administration procedure.[2]
- NGN-401 is an AAV9-based gene therapy incorporating EXACT™ transgene regulation technology designed to enable controlled MeCP2 expression on a cell-by-cell basis and is being evaluated for the treatment of Rett syndrome through delivery via ICV administration.[7]
- ICV delivery was selected based on preclinical biodistribution studies demonstrating broader biodistribution to the regions of the brain and nervous system that underlie Rett syndrome pathophysiology, compared to IT-L administration.[2,6]
- Here, we describe the rationale, ICV administration approach, and clinical tolerability in the Phase 1/2 (NCT05898620) trial of NGN-401 in participants with Rett syndrome, which has completed dosing.

METHODS

- Compared to IT-L*, ICV delivery has been shown to have greater biodistribution to the key areas of the brain and CNS that underlie Rett syndrome in preclinical models (**Figure 1**).
- These data confirm that ICV and IT-L* administration lead to comparable transduction of the peripheral organs; IT-L* did not show liver-sparing benefits compared with ICV.
- In the Phase 1/2 trial, ICV administration of NGN-401 (1E15 vg) was conducted under standard neurosurgical technique (**Figure 2**).

Figure 1. ICV delivery achieves greater expression in the brain and nervous system compared with IT-L* in non-human primates



*Administered in the Trendelenburg position.
AAV, adeno-associated virus; HED, human equivalent dose; ICV, intracerebroventricular; IT-L, intrathecal lumbar; RNA, ribonucleic acid.

Figure 2. In clinical trials, ICV administration of NGN-401 is aligned with standard neurosurgical technique

1 Pre-operative

PREPARATION

- Review MRI to plan optimal entry point
- Preparation of NGN-401 using aseptic technique
- Administer general anesthesia

2 ICV administration

CATHETER PLACEMENT & MEDICATION DELIVERY

- Neuronavigation is used to ensure proper catheter placement
- A single small burr hole is introduced into the skull
- Catheter is guided into the lateral ventricle
- CSF is aspirated (up to 10 mL)
- NGN-401 is delivered unilaterally with continuous intracranial pressure monitoring
- Administration takes approximately 10 minutes

3 Post-operative

RECOVERY

- Post-operative monitoring for up to 24 hours
- Post-operative CT scan

ICV administration is a safe and routine procedure chosen to optimize CNS coverage in gene therapy

CNS, central nervous system; CSF, intra-cerebrospinal fluid; CT, computed topography; ICV, intracerebroventricular; MRI, magnetic resonance imaging.

RESULTS

Efficacy

- As of the data cut off date of October 30, 2025, 10 participants (8 pediatric, 2 adolescent/adult) received NGN-401 (1E15 vg) via ICV administration.
- Of the 8 pediatric participants:
  - All participants showed functional improvements across core disease domains.
  - A total of 35 developmental milestones were gained, with no plateau up to 24 months.
  - 88% of participants achieved improved Clinical Global Impression-Improvement scores.

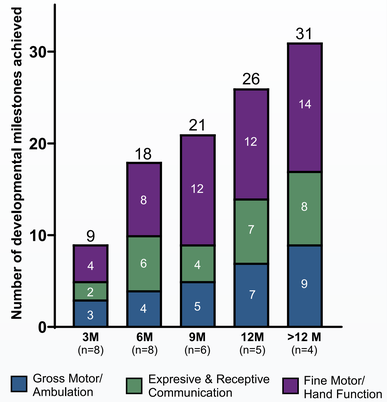
Safety

- The 1E15 vg dose and ICV procedure were generally well tolerated.

Phase 3 Registrational Trial

- The Embolden™ registrational trial is also utilizing ICV administration of NGN-401 for the treatment of Rett syndrome, and investigators are given the option of discharging participants one day after the ICV procedure and implementing an outpatient gene therapy monitoring protocol.

Figure 3. Interim Phase 1/2 data showed developmental milestones increased by domain over time following NGN-401 treatment in pediatric participants (n=8)



These data are as of the interim data cutoff date of October 30, 2025.

KEY CONCLUSIONS

1. ICV is a common neurosurgical procedure used for various therapeutics such as enzyme replacement, chemotherapy delivery, diagnostic access, and gene therapies.
2. In preclinical models, ICV delivery achieved greater biodistribution to key areas of the brain and nervous system, compared to IT-L administration.
3. In the Phase 1/2 trial investigating NGN-401 for the treatment of Rett syndrome, all 8 pediatric participants showed functional improvements, and the ICV procedure was generally well tolerated.
4. These findings, in conjunction with other therapeutic programs, support ICV as a safe and routine method for CNS-mediated gene therapy delivery with outpatient potential.

References

1. Pardridge WM. *NeuroRx* 2005; 2 (1): 3–14. **2.** Cohen-Pfeffer JL *et al. Pediatr Neurol* 2017; 67: 23–35. **3.** Data on File at Neurogene Inc. **4.** Gadalla KKE *et al. Mol Ther* 2013; 21: 18–30. **5.** Foust KD *et al. Nat Biotechnol* 2009; 27: 59–65. **6.** Burstein SR *et al*. Route Matters: Intracerebroventricular (ICV) Delivery of NGN-401 Drives Superior Transgene Expression to Key Areas of the Brain When Compared to Lumbar Intrathecal (IT-L) Delivery at a Clinically Relevant Dose – Implications for a One-Time Gene Therapy for Rett Syndrome. Poster presented at ESGCT 2025; Seville, Spain, 7–10 October 2025. **7.** Ross PJ *et al*. *Sci Transl Med* 2025; 17: eadq3614.

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