First-in-Human Study of NRTX-1001 GABAergic Interneuron Cell Therapy for the Treatment of Focal Epilepsy

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CIRM CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE (TRAN1-11611; CLIN2-13355)

NEURONA THERAPEUTICS

NTE001: Unilateral Drug-Resistant MTLE

NTE002: Bilateral Drug-Resistant MTLE

Rationale

GABAergic interneuron cell therapy offers a novel regenerative approach to the potential treatment of drug-resistant focal epilepsy that is not tissue-destructive. Administration of human cortical-type GABAergic interneurons into a chronic mouse model of MTLE results in robust and stable seizure suppression (Bershteyn et al., 2023 Cell Stem Cell). This clinical study is investigating whether one-time administration of human GABAergic interneurons derived from allogeneic human stem cells (NRTX-1001) is safe and can lead to seizure control in drug-resistant mesial temporal lobe epilepsy (MTLE). RMAT (Regenerative Medicine Advanced Therapy) designation granted in June 2024.

Methods

This first-in-human Phase I/II trial (NCT05135091) involves 10 subjects (ages 25–59) with drug-resistant unilateral MTLE and hippocampal sclerosis. Subjects received a single stereotactic hippocampal injection of NRTX-1001 (low dose: n=5; high dose: n=5) following 6 months of retrospective baseline seizure monitoring. Immunosuppression was initiated 1 week pre-surgery and tapered after 1 year. Primary and secondary endpoints included safety throughout the first year and seizure frequency reduction (months 7–12 post-administration). Baseline seizure frequency averaged 16/month (2–40) for all seizures and 8.3/month (2–32) for disabling seizures.

Seizure frequency, neuropsychological assessments, and adverse events are reported as of 20 November 2024.

Clinical Trial Design

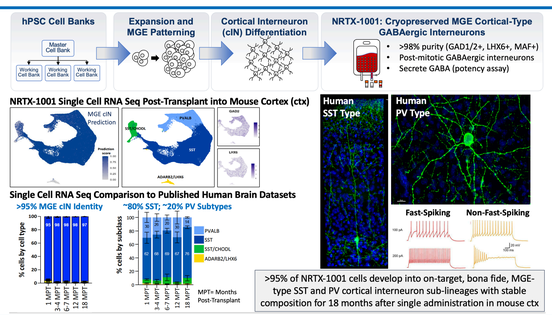
Key Inclusion Criteria*

- Male or Female, age ≥18 to 65
- Focal seizures, clinically defined as TLE
- Has failed to achieve seizure control despite adequate trials of at least 2 ASMs at appropriate doses
- Currently on stable doses (at least 1 month) of approved ASMs
- Single seizure focus confirmed, with MRI showing MTS and EEG telemetry consistent an anterotemporal onset
- Seizure frequency averages ≥2 per 28-day period over the 6 months prior to screening.
- If Dominant side focus, Verbal Learning <1.0 SD below mean

Key Exclusion Criteria

- Epilepsy due to other and/or progressive neurologic disease
- Significant other medical condition which would impair safe participation
- Primary or secondary immunodeficiency
- Suicide attempt in the past year
- Severe psychiatric disorders
- Chronic indwelling intracranial device (exception for RNS)
- MRI indicating potential malignant lesion
- Pregnancy, or currently breastfeeding

*Current protocol permits upper age bound of 75, requires a seizure frequency of 4 per 28-day period, and removes the Verbal Learning element



>95% of NRTX-1001 cells develop into on-target, bona fide, MGE-type SST and PV cortical interneuron sub-lineages with stable composition for 18 months after single administration in mouse ctx

Seizure Frequency

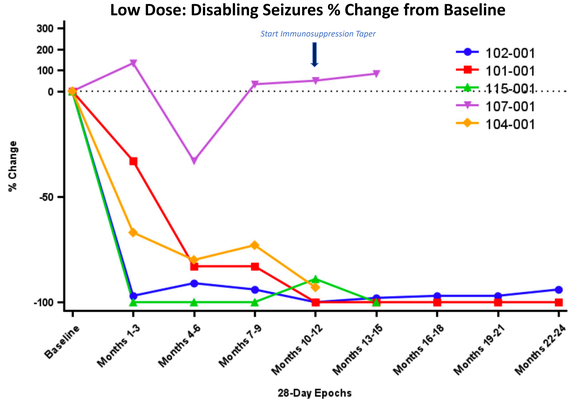
Cohort 1: Low Dose (n=5)

- 92% median seizure reduction for disabling seizures in Months 7 - 12
- 80% responder rate for >75% reduction in disabling seizures in Months 7 - 12
- The two subjects to date who discontinued immunosuppression at 1 year have maintained seizure control

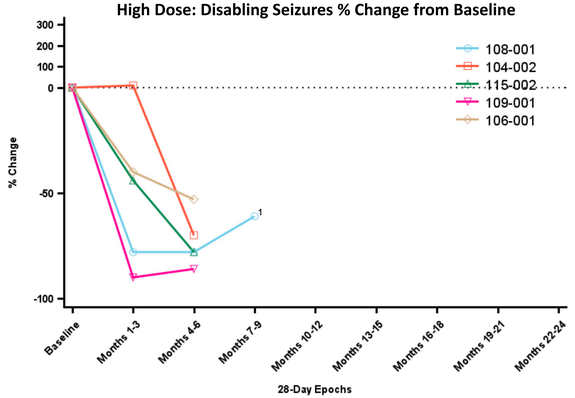
Cohort 2: High Dose (n=5)

- 78% median seizure reduction for disabling seizures in Months 4 - 6
- 60% responder rate for >75% reduction in disabling seizures in Months 4 - 6

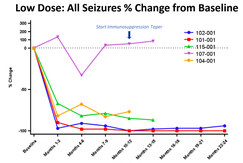
Low Dose: Disabling Seizures % Change from Baseline



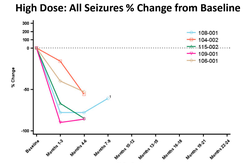
High Dose: Disabling Seizures % Change from Baseline



Low Dose: All Seizures % Change from Baseline



High Dose: All Seizures % Change from Baseline



[1]Epoch contains a cluster of ~50 focal aware with objective signs seizures

All Seizure Events = Focal Aware Without Objective Signs, Focal Aware With Objective Signs, Focal Impaired Awareness, Focal to Bilateral Tonic Clonic, and Other Seizures

Disabling Seizures = Focal Aware With Objective Signs, Focal Impaired Awareness, Focal to Bilateral Tonic Clonic, and Other Seizures

Neuropsychological Assessments

Cohort 1: Low Dose (n=5)

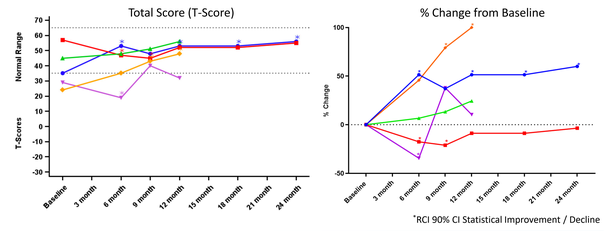
Cognition and QOL scores are generally maintained or increased

Increased scores from baseline detected for some subjects:

- 2 of 5 subjects increased on BNT word retrieval
- 2 of 5 subjects increased on RAVLT delayed recall
- 1 of 5 subjects increased on BVMT delayed recall
- 3 of 5 subjects increased on QOLIE overall quality-of-life

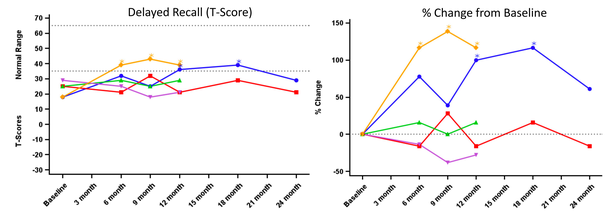
102-001 ND
101-001 ND
115-001 D
107-001 D
104-001 ND

BNT - *Word Retrieval*



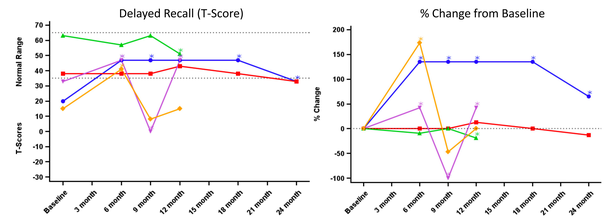
*RCI 90% CI Statistical Improvement / Decline

RAVLT - *Verbal Memory*



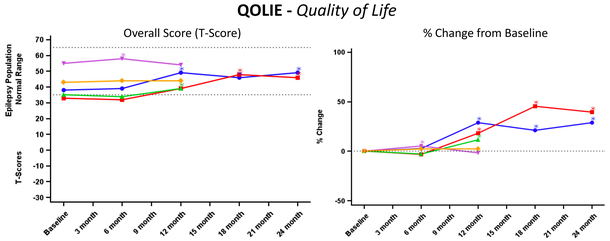
*RCI 90% CI Statistical Improvement / Decline

BVMT - *Visuospatial Memory*



*RCI 90% CI Statistical Improvement / Decline

QOLIE - *Quality of Life*



*MIC 5 Points Improvement / Decline

BNT = Boston Naming Test. RAVLT = Rey Auditory Verbal Learning Test.
BVMT = Brief Visuospatial Memory Test. QOLIE = Quality of Life in Epilepsy
RCI = Reliable Change Index. MIC = Minimal Important Change
D = Dominant Hemisphere Seizure Onset. ND = Non-dominant Hemisphere Seizure Onset

Adverse Events

- **No Adverse Events determined to be related to the cells.**
- No structural abnormalities on quarterly follow up MRI scans.
- Mild to moderate AEs (non-serious) related to the procedure and immunosuppression.
- Immunosuppression AEs resolved in the two subjects who discontinued immunosuppression.
- Two subjects experienced SAE of status epilepticus that were consistent with their prior medical history and thus determined to be related to their underlying condition

List of Adverse Events Reported in at Least Two Subjects

System Organ Class / Preferred Term		Number of Subjects All	Low Dose	High Dose
Blood and lymphatic system disorders:				
Anemia		2	2	0
Gastrointestinal disorders:				
Constipation		2	1	1
Diarrhea		5	2	3
Vomiting		2	1	1
General disorders and administrative site conditions:				
Fatigue		2	1	1
Nervous system disorders:				
Dizziness		3	1	2
Headache		3	1	2
Status epilepticus		2	1	1
Syncope		2	1	1
Tremor		5	4	1
Renal and urinary disorders:				
Acute kidney injury		3	2	1

List of All Serious Adverse Events Reported

System Organ Class / Preferred Term		Number of Subjects All	Low Dose	High Dose
Nervous system disorders:				
Status epilepticus		2	1	1
Renal and urinary disorders:				
Acute kidney injury		1	1	0

Summary

- NRTX-1001 is a differentiated post-mitotic inhibitory interneuron cell therapy
- Cells administered into hippocampal seizure focus

Safety Outcomes:

- No significant surgical complications or cell-related adverse events
- Mild immunosuppression-related events, all resolved after discontinuation
- Stable or improved memory and quality-of-life scores
- No structural abnormalities detected on follow-up scans

Seizure Control Outcomes:

- Low Dose: 92% median monthly reduction and 80% responder rate for ≥75% reduction in disabling seizures, months 7 - 12
- High Dose: 78% median monthly reduction and 60% responder rate for ≥75% reduction in disabling seizures, months 4 – 6

Ongoing Clinical Studies

- Additional Expansion for Cohorts 1 & 2 underway
- Cohort 3 [Non-MTS] Open – Subjects with single seizure focus confirmed by PET hypometabolism and EEG telemetry (10 subjects)
- NTE002 (NCT06422923) Open – A Study of Inhibitory Interneurons for the Treatment of Drug-resistant Bilateral Temporal Lobe Focal Seizures (10 subjects)

For additional information:
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