First-in-Human Trial of NRTX-1001 GABAergic Interneuron Cell Therapy for Treatment of Focal Epilepsy - Emerging Clinical Trial Results

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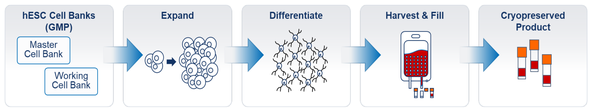
INTRODUCTION

- Many people with mesial temporal lobe epilepsy continue to have seizures despite use of anti-seizure drug therapy
- Using inhibitory interneurons as a cell therapy to reduce seizures is a novel strategy to provide targeted inhibition to hyperexcitable neural networks in the epileptic brain
- NTRX-1001 cellular therapeutic comprises GABAergic, post-mitotic interneurons of a specific pallial-type lineage derived from human pluripotent stem cells
- A multicenter, dose-escalation phase I/II clinical trial has been launched to evaluate NRTX-1001 in people with pharmacoresistant temporal lobe epilepsy (TLE)

NRTX-1001 Manufacturing for Clinical Use

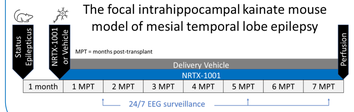


- NRTX-1001 is an allogeneic, cryopreserved cellular therapeutic intended for single administration and long-term persistence in the clinical population in drug-resistant mesial temporal lobe epilepsy (MTLE)
- NRTX-1001 has high purity: >98% medial ganglionic eminence (MGE) pallial-type GABAergic interneurons
- NRTX-1001 cells are post-mitotic: The interneurons are not proliferative or cycling cells detected
- NRTX-1001 manufacturing is reproducible: 3 of 3 lots of cGMP clinical product passed all release criteria (safety, identity, strength, purity, and composition); sufficient for dosing all subjects in Phase I/II trial

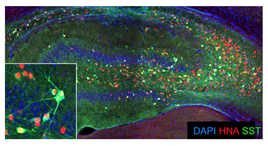
NRTX-1001 Transplantation Reduces Focal Electrographic Seizure Frequency and Reduces Pathology in Epileptic Mice

Preclinical Model of Temporal Lobe Epilepsy

The focal intrahippocampal kainate mouse model of mesial temporal lobe epilepsy

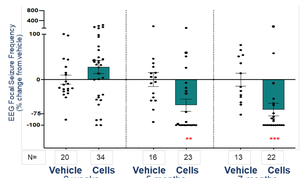


NRTX-1001 Cell Fate and Persistence



At 7 months post-transplant, NRTX-1001 persist in the epileptic hippocampus (Human Nuclear Antigen, red), and express the MGE-type GABAergic neuronal marker LHX6 (green) and interneuron subtype marker somatostatin (SST; green)

Seizure Frequency and Responder Rate

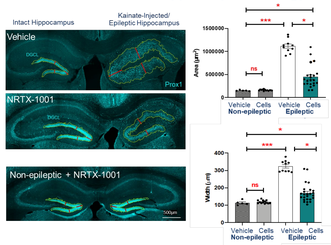


Treatment	Electrographic Seizure Frequency at 7 MPT (Median)	# Animals with >95% seizure reduction at 5 MPT Fraction (Percent)	# Animals with >95% seizure reduction at 7 MPT Fraction (Percent)
Vehicle			
NRTX-1001			

Fisher's exact test *P<0.05, ***P<0.001

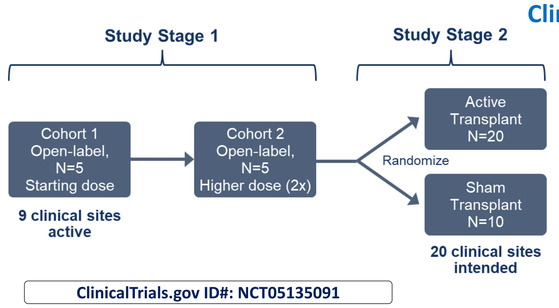
By 5 months post-transplant, seizure frequency is significantly reduced in epileptic animals that received NRTX-1001.

NRTX-1001 Reduces Hippocampal Pathology



At 7 months post-transplant, dentate granule cell dispersion in the hippocampus is significantly reduced in epileptic animals that received NRTX-1001.

Clinical Administration of NRTX-1001

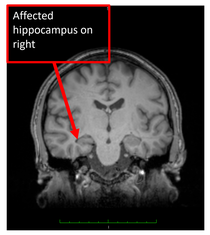


ClinicalTrials.gov ID#: NCT05135091

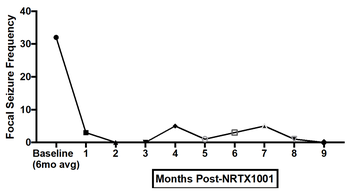
- **Design**: This study is designed as a multicenter dose escalation study in which subjects with unilateral mesiotemporal lobe epilepsy (MTLE) with hippocampal sclerosis and focal seizures that are refractory to drug treatment receive a single administration of NRTX-1001 into the hippocampal seizure focus, using stereotactic MRI-guided delivery. Subjects receive immunosuppression
- **Primary Endpoint**: Safety. Frequency of adverse events
- **Secondary Endpoint**: Efficacy
- **Testing Platforms**: EEG, imaging, assessment of visual fields, tests of memory, mood, and Quality of Life measures
- **Assessments of Activity:** Reduction in seizure frequency and severity; reduction in anti-seizure drug doses; improvements on Quality of Life measures, neuropsychological outcomes, memory; MRS-imaging biomarkers

First subject treated in June 2022

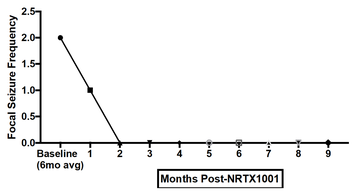
- Adult with 9-year history of seizures
- **Averaging 32 seizures/month** in the 6 months prior to screening
  - **30 focal aware seizures per month**
  - **2 focal impaired awareness seizures per month**
- Had failed to gain seizure control with use of four different anti-seizure medications
- EEG confirms right hippocampal onset
- MRI shows right hippocampal sclerosis



All Seizure Events per Month



Impaired Awareness Seizures per Month

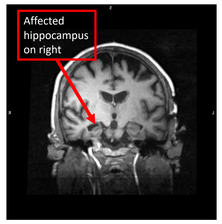


		Normal Adult	Baseline	6-month	9-month
Word Retrieval	Boston (total score)	54 +/- 4	50	57	55
Verbal Learning and Memory	RAVLT sum #correct trials 1-5	46 +/- 10	27	34	34
	RAVLT #correct 6	5 +/- 2	3	5	3
	RAVLT item 7 (delayed recall)	9 +/- 3	2	7	7
	RAVLT item 8 (delayed recall)	9 +/- 3	2	6	4
Visuospatial Memory	BVMT delayed recall score	10 +/- 2	6	10	10
	BVMT % retained	93 +/- 10%	67%	91%	100%

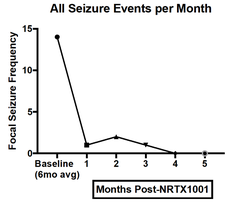
NRTX-1001 has been well-tolerated, resulting a 94% reduction and elimination of impaired-awareness seizures

Second subject treated in Oct 2022

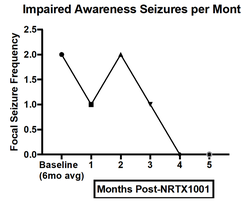
- Adult with 8-year history of seizures
- **Averaging 14 seizures/month** in the 6 months prior to screening
  - **12 focal aware seizures per month**
  - **2 focal impaired awareness seizures per month**
- Had failed to gain seizure control with use of 3-4 different anti-seizure medications
- EEG confirms right temporal lobe
- MRI shows right hippocampal sclerosis



All Seizure Events per Month



Impaired Awareness Seizures per Month



Data are reported as of 13 March 2023

NRTX-1001 has been well-tolerated, resulting a 94% seizure reduction

CONCLUSIONS

- NRTX-1001 is a highly-pure, clinical-grade, allogeneic cellular therapeutic comprising post-mitotic MGE-type GABAergic interneurons
- In the intrahippocampal kainate mouse model of chronic mesial temporal lobe epilepsy, NRTX-1001 transplantation reduces focal electrographic seizures and hippocampal pathology. After dosing, NRTX-1001 persist long-term, distribute and integrate within the hippocampus, and do not cause neuroinflammation, ectopic tissue formation, or the development of toxicities.
- The first-in-human study of NRTX-1001 GABAergic interneurons for focal temporal lobe epilepsy is underway to explore the clinical safety and activity of NRTX-1001 in people with chronic temporal lobe epilepsy (NCT05135091). Recruitment for additional subjects in the open-label dose escalation (Stage 1) is ongoing.
- Preliminary results are encouraging. NRTX-1001 may be a non-destructive therapeutic option for patients with temporal lobe epilepsy that originates in the dominant or non-dominant hippocampus who do not choose to undergo resection, and for those with bilateral temporal lobe epilepsy.

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