Trajectory selection and procedural considerations for the first-in-human delivery of AMT-260, an investigational gene therapy for medically refractory mesial temporal lobe epilepsy

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Background

Mesial temporal lobe epilepsy (MTLE) is the most common focal epilepsy

Figure 1. Epidemiology and Drug Resistance of MTLE

- **~60%** of epilepsies are focal
- **>60%** of focal epilepsies are TLE[1,2]
- **80%** of TLE affects the mesial temporal lobe[3]

Drug Resistance is Prevalent in Epilepsy:

- **30%** of all epilepsies are drug resistant
- **75%** are resistant when MRI identifies hippocampal sclerosis[4]

MRI, magnetic resonance imaging; MTLE, mesial temporal lobe epilepsy; TLE, temporal lobe epilepsy.

Highly effective surgical treatments are underused

- Traditional resection and Laser Interstitial Thermal Therapy (LITT) are both highly effective
- Patient and clinician perception of operative risks reduces utilization

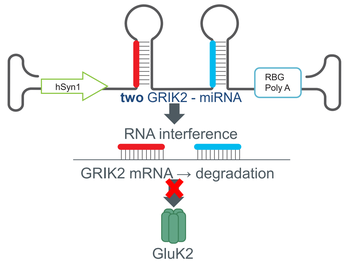
Gene therapies are currently being investigated

- Hippocampal hyperexcitability is reduced by targeting specific molecular mechanisms
- AMT-260 uses microRNA (miRNA)-mediated silencing to target the GluK2 kainate receptor

Gene therapy delivery presents unique procedural considerations compared with LITT

AMT-260: An AAV9 Gene Therapy Targeting GluK2

Figure 2. AMT-260 Mechanism of Action



AAV, adeno-associated virus; miRNA, microRNA; mRNA, messenger RNA; hSyn1, human synapsin 1 promoter.

- AMT-260 is a recombinant AAV9 coding for two engineered miRNAs which interfere with GRIK2 mRNA[5,6]
- Interference reduces the expression of the GluK2 glutamate receptor subunit[5,6]
- This leads to a reduced expression of kainate-type glutamate receptors containing the GluK2 subunit[5,6]

Clinical Trial of AMT-260:

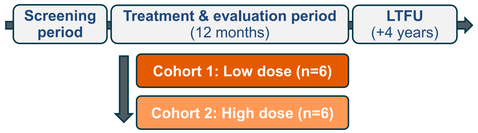
GenTLE Gene Therapy in TLE

First-in-human phase I/IIa trial (NCT06063850)

- A multicenter study of safety, tolerability, and preliminary efficacy (**Figure 3**)
- **Participants are adults with unilateral refractory MTLE**

Figure 3. GenTLE Phase I/IIa Trial Design

Objective: Evaluate the safety, tolerability, and preliminary signs of efficacy of AMT-260 in adults with unilateral refractory MTLE and a baseline mean of ≥2 focal impaired awareness seizures per month



LTFU, long-term follow-up; MTLE, mesial temporal lobe epilepsy.

Cohorts:

- Two dose cohorts of six participants each

Intervention:

- Single intracerebral administration of AMT-260
- Dose volume based on one third of hippocampal volume
  - Range: 643 µL to 1419 µL

Delivery method:

- Convection-enhanced delivery (CED)
- Single stereotactic trajectory
- Performed under magnetic resonance imaging (MRI) guidance

Table 1. Key Primary and Secondary Endpoints

Primary:	Secondary:
• Incidence of AEs • Tolerability	• Vector and miRNA biodistribution, vector shedding • Early signs of efficacy • Neuropsychology

AE, adverse events; miRNA, microRNA.

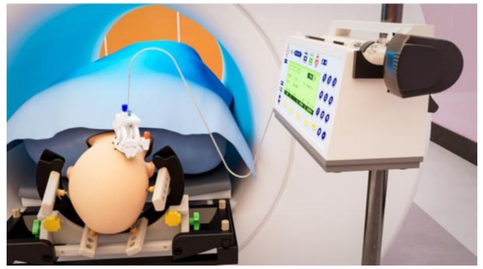
You can search **GenTLE** on clinicaltrials.gov: **NCT06063850**

Administration

Single occipital trajectory to the hippocampus (Figures 4 and 5)

- Single stereotactic administration into the hippocampus with MRI-guided CED via an occipital trajectory
- Trajectory prioritizes coverage of the hippocampal head and body
- Trajectory chosen by treating surgeon and neurosurgical steering committee

Figure 4. Unilateral Infusion of AMT-260 Using MRI-Guided CED via 16g ClearPoint SmartFlow Cannula

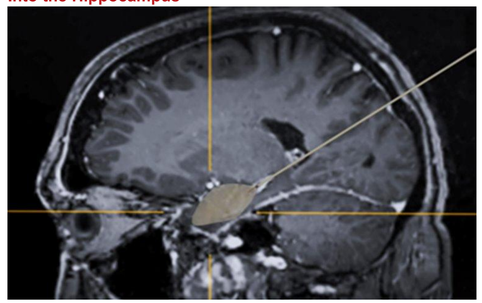


CED, convection-enhanced delivery; MRI, magnetic resonance imaging.

Gene therapy procedural considerations vs LITT

- Similar trajectories with different goals and constraints
- Coverage depends on convective distribution rather than thermal spread
- Finite drug volume delivered over a finite infusion window
- Distribution reduced by perivascular leakage and cerebrospinal fluid (CSF) loss
- Intraoperative MRI tracking of co-infused gadolinium enables distribution monitoring and intraprocedural adjustment

Figure 5. Single Stereotactic Administration of AMT-260 Into the Hippocampus



Results (May 29, 2026 cut-off date)

Table 2. Baseline Demographics and Disease Characteristics

Population Characteristics	Cohort 1: Low dose (n=6)
Age (years), median (range)	52 (36, 61)
Male, n (%)	4 (67)
BMI (kg/m^2), median (range)	30 (19, 32)
Dominant TLE, n (%)	3 (50)
Mesial temporal sclerosis, n (%)	3 (50)
Duration of epilepsy (years), median (range)	16 (8, 55)
Baseline disabling seizures per 28 days, median (range)	7 (5, 14)
Baseline antiseizure medications, median (range)	3 (2, 4)

BMI, body mass index; TLE, temporal lobe epilepsy.

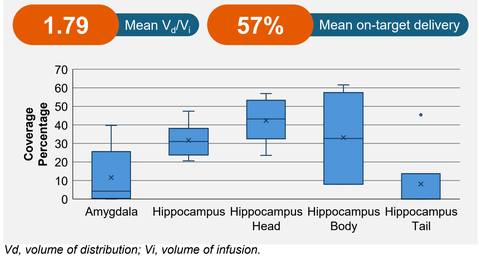
SAFETY:

- **Adverse Events (AEs)**
  - AEs were reported in 4 of 6 participants; 16 were Grade 1 and 5 were Grade 2 severity, with headache most common (n=2)
  - AEs were considered by investigators to be related to the AMT-260 neurosurgical procedure (48%) or AMT-260 (19%)
- **No SAEs, dose-limiting events, or AEs leading to study discontinuation**
- **No clinically significant catheter-related hemorrhage** or new neurological deficits

COVERAGE RESULTS:

- CED with controlled incremental flow rates (1–10 µL/min) achieved anatomical distribution with minimal reflux
- Mean hippocampal coverage
  - Hippocampal head: 42% (range 24–57%)
  - Hippocampal body: 33% (range 8–62%)

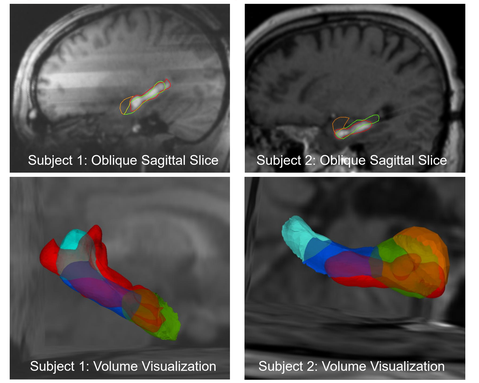
Figure 6. Coverage Statistics by Target



Vd, volume of distribution; Vi, volume of infusion.

COVERAGE RESULTS (continued)

Figure 7. Visualizations of Hippocampal Infusions



Slice Outlines:
Green: Hippocampus
Orange: Amygdala
Red: Detected infusion

3D Outlines:
Green: Hippocampus head
Blue: Hippocampus body
Light blue: Hippocampus tail
Orange: Amygdala
Red: Detected infusion

CONCLUSIONS

- As of May 29, 2026 cutoff date, AEs were reported in 4 of 6 participants; 16 were Grade 1 and 5 were Grade 2 severity, with headache most common (n=2)
- Occipital approach enables anatomical coverage of the hippocampal head and body via a single trajectory
- Precise trajectory planning and use of CED are critical for successful administration of gene therapies in MTLE
- Optimizing target coverage is vital for the reproducibility of results as gene therapies move toward pivotal late-stage clinical trials
  - Proper selection of trajectory
  - Accuracy of targeting
  - Active management of perivascular/CSF loss during CED

REFERENCES

1. Semah F, et al. *Neurology*. 1998;51(5):1256-1262. **2.** Téllez-Zenteno JF, et al. *Epilepsy Res Treat*. 2012;2012:630853. **3.** Tatum WO, et al. *J Clin Neurophysiol*. 2012;29(5):356-365. **4.** Pohlen MS, et al. *Epilepsy Res*. 2017;137:56-60. **5.** Boileau C, et al. *Ann Neurol*. 2023;94(4):745-761. **6.** Baudouin S, et al. *Mol Ther Methods Clin Dev*. 2024;32(4):101342.

Disclosures: *AMT-260 is an investigational agent that has not been approved by the US Food and Drug Administration or any other regulatory health authority. The safety and efficacy of AMT-260 for any use has not been established. There is no guarantee that investigational agents will receive health authority approval or become commercially available.*

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