PatiEnt Neuropsychological outcomeS After laseR ablation

NCT05075850
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PENSAR
LAANTERN
REGISTRY

PROTOCOL SIGNATURE PAGE

PatiEnt Neuropsychological outcomeS After laseR ablation

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and my hospital institutional review board (IRB). I will discuss this material with them and ensure the conduct of the study according to this protocol, including applicable laws, regulatory requirements, general standards of good clinical practice and any other instructions provided by the Sponsor and the IRB.

_____
Site Name

_____
Site Investigator (Printed Name)

_____
Site Investigator (Signature)

_____
Date

TABLE OF CONTENTS

1 DEFINITIONS

Term	Definition
Comprehensive neuropsychological assessment	Defined by AACN guidance (Board of Directors, 2007): *"Neuropsychological evaluations vary in content depending on their purpose, but they typically assess multiple neurocognitive and emotional functions. Primary cognitive domains include: intellectual functions; academic skills (e.g., reading, writing, math); receptive and expressive language skills (e.g., verbal comprehension, fluency, confrontation naming); simple and complex attention; learning and memory (e.g., encoding, recall, recognition); visuospatial abilities; executive functions, problem-solving and reasoning abilities; and sensorimotor skills. Ideally, assessments should also include measures designed to assess personality, social-emotional functioning, and adaptive behavior."*
Cognitive Domain	For this study, collected cognitive domains include Language, Executive Function, Attention, Verbal Memory, Visual Memory, Verbal Fluency, and Motor Function
Preferred neuropsychological tests	For this study, tests include Boston Naming, Trails making Test A and Test B, Digit Span, Logical memory test (subtest from Wechsler Memory Scale IV), BVMT--Brief Visuospatial Memory Test, Animal Fluency test, and Grooved Pegboard
LAANTERN registry	ClinicalTrials.gov identifier NCT02392078, Protocol CL10027
LAANTERN Index Procedure	First NeuroBlate® System procedure after signing the LAANTERN Informed Consent Form.
Protocol Deviation	An event that did not occur according to the protocol and which will include issues with consenting and missed follow-up Neuropsychology testing.
Visual field testing	Humphry Automated fields for visual field testing to assess peripheral vision.

2 BACKGROUND & PURPOSE

A portion of patient concern regarding epilepsy surgery is potential for cognitive decline or functional deficit following surgery. To address this concern, comprehensive neuropsychological testing is performed as part of the surgical epilepsy evaluation and at follow-up. While neuropsychological and functional change after open resection is well described, change following Laser Interstitial Thermal Therapy (LITT) is less well known. The goal of this study is to assess and describe differences in post-surgical neuropsychological test scores in a population of patients with epilepsy who are undergoing LITT. This study will also assess a subset of patients with mesial temporal lobe epilepsy for changes to visual fields. This study is being conducted as a sub-study within the LAANTERN registry; therefore, all enrolled patients in PENSAR must be consented to both protocols.

3 INTERVENTION/TREATMENT

- All subjects will undergo comprehensive neuropsychological assessment post-LITT per standard of care practice.
- Visual field testing will be conducted in a subset of enrolled patients.

4 STUDY DESIGN OVERVIEW

This is a multicenter sub-study that will include comprehensive neuropsychological assessment data collection done at baseline (within 1 year prior to the index LITT procedure) and at follow-up (at least 6 months from the index LITT procedure). Visual field testing will be conducted in a subset of enrolled patients. Up to 250 subjects may be enrolled at up to 15 study sites.

4.1 STUDY OBJECTIVES

Primary outcome measure: Site-determined cognitive changes per domain

[Time Frame: 6+ months]

Neuropsychological test data will be collected for all study participants to describe cognitive domain specific changes as a cohort. Change will be assessed from raw test scores and demographically corrected standardized scores (where available).

Secondary outcome measure 1: Change in raw test scores from standard battery of preferred neuropsychological tests

[Time Frame: 6+ months]

Describe the observed change or stability of neuropsychological test scores in patients who underwent laser ablation surgery. Change will be assessed from raw test scores and demographically corrected standardized scores (where available).

Secondary outcome measure 2: Incidence of visual field deficits in patients with MTLE.

[Time Frame: 6+ months]

Visual field testing using Humphry automated fields (HVF 24-2 SITA standard) will be conducted for a subset of patients to identify visual field deficits resulting after the LITT procedure.

4.2 STUDY POPULATION

Subjects who meet inclusion criteria and no exclusion criteria and sign the Informed Consent Form (ICF) (CL10149) will be considered enrolled in this study. Subjects will continue to be identified by their unique identification number (ID) assigned in LAANTERN and will be presented with additional electronic Case Report Forms (eCRFs) applicable for the PENSAR study.

Inclusion Criteria:

1. Patient or legally authorized representative provides written authorization and/or consent.
2. Patient is enrolled in the LAANTERN trial and had an epilepsy diagnosis without the presence of a malignant brain tumor.
3. Patient is 16 years of age or older.
4. Patient has completed a baseline comprehensive neuropsychological assessment with a neuropsychologist.

Exclusion Criteria:

1. Patient does not complete the index LITT procedure as specified in the LAANTERN registry.

5 INFORMED CONSENT (ICF)

The Sponsor will provide a template ICF to each site for Institutional Review Board (IRB) submission prior to the site initiation. This template may be modified to suit the requirements of the individual study site. The Sponsor must pre-approve all changes to the ICF prior to initial submission to the IRB. A copy of the IRB-approved ICF must be sent to the Sponsor and the original copy must be retained at the study site. If the ICF is amended by the reviewing IRB, the Sponsor must pre-approve all changes to the ICF prior to submission. In addition, a copy of the approved documents must be provided by the Investigator to the Sponsor prior to enrollment of subjects in the study.

The Investigator or assigned designee must administer this approved ICF to each prospective study subject and obtain the subject's signature or a legally authorized representative signature along with the date of consent and prior to performing any PENSAR study related activity. The ICF must be obtained in accordance with 21 CFR Part 50. Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and informed that withdrawal from the study will not jeopardize their future medical care. A copy of ICF must be given to each subject enrolled in the study. The institutional standard subject consent form does not replace the study ICF.

6 VISIT SCHEDULE AND DATA COLLECTION

Neuropsychological testing is typically conducted as standard of care at baseline and at follow-up. The testing should be conducted by qualified neuropsychologist. The neuropsychologist should use the same tests at follow-up so that the status of change from baseline may be assessed.

Collection of preferred test results will allow for pooling of multicenter data for the Primary Outcome and Secondary Outcome 1. A listing of preferred and commonly used tests assessing multiple neuropsychological functions are provided in **Table 1**.

Additional neuropsychological tests consisting of each site's standard-of-care battery (along with raw scores and demographically corrected standardized scores) will also be accepted in cases where preferred test results are not available.

Visual fields testing will be conducted as the study intervention/treatment at follow-up using Humphry automated fields (HVF 24-2 SITA standard) for visual field testing to assess peripheral vision after at least 6 months from the index LITT procedure in cases where:

- The patient is diagnosed with mesial temporal lobe epilepsy (MTLE)/mesial temporal sclerosis (MTS).
- The patient has an amygdala/hippocampal LITT ablation.

- The patient is surgically naïve prior to the LITT procedure (excluding surgical placement of diagnostic electrodes).
- The patient does not have glaucoma or other known retina/eye issues that would interfere with Visual field testing or interpretation of the results.

Single field Analysis result from both eyes and summary data of normal/abnormal findings will be collected.

Figure 1: Study Flow Chart

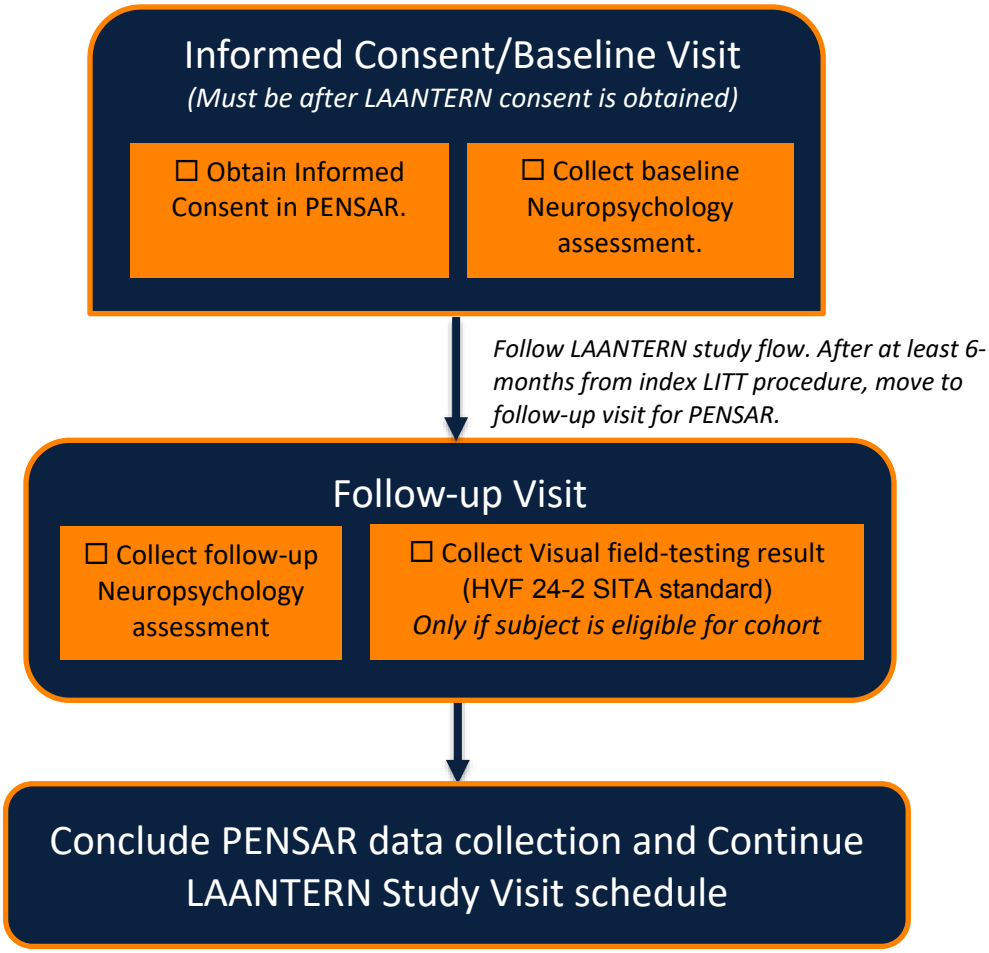

Table 1: Comprehensive Neuropsychological Testing	
Preferred Neuropsychological tests *(Secondary outcome measure 1)*	**Cognitive domain** *(Primary outcome measure and Secondary outcome measure 1)*
1. Boston Naming	Language
2. Trails making Test A and Test B	Executive Function*
3. Digit Span	Attention*
4. Logical memory test (subtest from Wechsler Memory Scale IV)	Verbal Memory
5. BVMT--Brief Visuospatial Memory Test	Visual Memory
6. Animal Fluency test	Verbal Fluency
7. Grooved Pegboard	Motor Function
*Components of Verbal Memory	

Table 2: Study Visit Schedule*		
	Baseline (within 1 year prior to the index LITT procedure)	**Follow-up** (At least 6 months from the index LITT procedure)
Inclusion/Exclusion Assessment	X	-
Comprehensive neuropsychological testing (See **Table 1**)	X†	X‡
Collection of preferred test scores:		
• *Boston Naming*	X	X
• *Trails making Test A and Test B*	X	X
• *Digit Span*	X	X
• *Logical memory test (subtest from Wechsler Memory Scale IV)*	X	X
• *BVMT--Brief Visuospatial Memory Test*	X	X
• *Animal Fluency test*	X	X
• *Grooved Pegboard*	X	X
If applicable, collection of change in substituted (non-preferred)§ test scores	-	X
Visual field testing‖	-	X
End of Study	Patient participation in the study will end after applicable follow-up testing is completed or upon subject withdrawal.	

*The visit schedule is calculated from the date of the LITT procedure captured under the LAANTERN protocol.
†Baseline testing is conducted as standard of care and is required to meet inclusion criterion 4.
‡If applicable, any patient-reported subjective memory changes are collected.
§If the preferred neuropsychological tests were not assessed at baseline, other comparable tests may be substituted; however, only the change in score will be collected at follow-up.
‖Visual fields will be assessed and collected only in cases where:

- The patient is diagnosed with mesial temporal lobe epilepsy (MTLE)/mesial temporal sclerosis (MTS).
- The patient has an amygdala/hippocampal LITT ablation.
- The patient is surgically naïve prior to the LITT procedure (excluding surgical placement of diagnostic electrodes).
- The patient does not have glaucoma or other known retina/eye issues that would interfere with Visual field testing or interpretation of the results.

7 STUDY COMPLETION OR WITHDRAWAL

Subjects will complete the PENSAR study once follow-up comprehensive neuropsychological testing is completed and/or their participation in the LAANTERN registry ends.

8 ADVERSE EVENT REPORTING

No separate adverse events will be collected or reported for this study. Adverse events will continue to be collected and reported under the LAANTERN protocol criteria and definitions. Visual field test results and neuropsychological outcomes are not reportable adverse events unless they meet LAANTERN protocol criteria and definitions.

9 PROTOCOL DEVIATIONS

Anticipated protocol deviations include improper consenting of subject (i.e., consent not obtained and improper consenting) and not completing follow-up neuropsychological testing. All deviations will be reported to Monteris Medical. It is the site's responsibility to report deviations in compliance with their Institutional Review Board if required.

10 DATA ANALYSIS

Study objectives will not be statistically powered given the anticipated heterogeneity in available neuropsychological test results.
Scores will be collected to assess domain specific changes for the Primary outcome measure using pre-defined clinically meaningful cut scores (based on previously described methods[1,2]):

- Changes of 1.5 standard deviations will be considered improved (+) or worsened (-).
- Changes of 2.5 standard deviations will be considered substantial post-operative improvements (+) or worsening (-).
- Any score change less than 1.5 standard deviation will be considered unchanged and the result of anticipated variability.

Descriptive statistics will be used to summarize the results for Secondary Outcome measures:

- Continuous variables: The total count, mean, standard deviation, minimum, and maximum will be provided.
- Categorical variables: Total count and percentage will be provided.

Ad hoc, exploratory analyses may be conducted if sufficient sample size allows for correlation or multivariate assessment of patient subsets (e.g., those with improvement or worsening).

11 DATA COLLECTION AND MANAGEMENT

The study will be performed in accordance with all requirements set forth in the U.S. regulations, 21 Code of Federal Regulations (CFR) Parts 50 (Protection of Human Patients), 56 (Institutional Review Board), and applicable requirements from the reviewing IRB for the study at each site.

The study data will be hosted in the same electric data capture (EDC) system as the LAANTERN registry where it will continue to follow compliance with the U.S. regulations, 21 CFR part 11, Electronic Records; Electronic Signatures.

All required data for this study will be collected on standardized Case Report Forms (CRFs).

Qualified study staff at each investigational site will perform primary data collection drawn from source document (e.g., hospital chart) review. All CRFs will be subject to review for omitted data, gross data inconsistencies, illegible data, and deviations. Any deficiencies or deviations will be reviewed, and any necessary action determined (e.g., data query, communication to the study center).

De-identified source documents will be collected for neuropsychological testing results at baseline and follow-up. De-identified source for the Single Field Analysis (HVF24-2 printouts) from both eyes will be collected as well as summary data of normal/abnormal findings.

Data review (including crosschecks) will be performed, and any discovered errors will be reported to the study site using the data correction and query process (as necessary). The study site will review the query, respond, and make any necessary corrections or comments. The data cleaning cycle will be repeated until all data are considered clean.

12 ADMINISTRATIVE RESPONSIBILITIES

12.1 SPONSOR RESPONSIBILITIES

The Sponsor's responsibilities for this study are to:

- Select qualified clinical investigators and study sites
- Provide study protocol training to participating study sites including the Investigator and staff conducting the study
- Provide financial support to each study site which is fair, reasonable, and equitable to fair market value
- Follow/promote all applicable regulatory standards per CFRs at each study site
- Own and control the use of the data, including review and approval of study-related publications/presentations, etc.

12.2 INVESTIGATOR RESPONSIBILITIES

The Primary Investigator for each site is responsible for ensuring the study is conducted according to:

- All signed agreements (including financial disclosures)
- The Study Protocol
- IRB guidelines
- Applicable Food and Drug Administration (FDA) regulations

The Investigator for each site may not begin enrollment until Sponsor receives and approves (when necessary) required documents, including a completed and signed Investigator Agreement/Clinical Trial Agreement (or equivalent), Protocol Signature Page, IRB and ICF approvals.

It is acceptable for the Investigator to delegate one or more of the above functions to an associate or Sub-Investigator or trained Study Coordinator; however, the Investigator remains responsible for the proper conduct of the clinical investigation, including obtaining and documenting proper study informed consent, collecting all required data, submitting accurate and complete CRFs, etc.

At each site, appropriate procedures must be followed to maintain subject confidentiality according to appropriate local regulations (e.g., Health Insurance Portability and Accountability Act in the U.S.). Each site may have its own internal procedures or requirements for use and release of subject medical information in research studies. Each Investigator is responsible for obtaining appropriate approvals, consents, or releases of medical information as dictated by their relevant patient privacy laws.

The study is not transferable to other sites attended by the Investigator unless prior approval is obtained from the appropriate IRB and the Sponsor.

12.3 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL

Investigators must submit the study protocol and ICF to their reviewing IRB and obtain IRB written approval before being allowed to conduct and participate in the study. Each Investigator must submit to the Sponsor a copy of the IRB approval letter, specific to this protocol and addressed to Investigator, certifying study approval prior to enrolling subjects into the study. This approval letter should identify the study name, study protocol number (including revision number), the date of the approval as well as the expiration date of such an approval. The Investigator is also responsible for fulfilling any conditions of approval imposed by the IRB, and for maintaining continuation of the approval during the entire study period. The Investigator must provide the Sponsor with copies of such approvals.

12.4 CONFIDENTIALITY

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject.

13 MONITORING

The Sponsor or a Sponsor representative will monitor the progress of the study as described in the Study Monitoring Plan. The Investigator consents to visits by the staff of the Sponsor or its representatives to review the study subject medical records, including any test or laboratory data that might have been recorded on diagnostic test media (e.g., MRI). The Sponsor will request that any source documents to be submitted to the sponsor, sponsor representative be de-identified (subject's name and other personal identifiers must be removed and replaced with the study subject ID).

14 INVESTIGATOR REPORTS AND RECORDS REQUIREMENTS

The Investigator is responsible for the completion and submission to the Sponsor of all CRFs and deviations from the protocol. If any action is taken by an IRB with respect to the study, the information must be forwarded to the Sponsor in a timely manner. All data must be stored and retained by the investigative site for a minimum of 2 years following a notification from Sponsor that all investigative sites are complete, terminated, or discontinued. Should the investigator withdraw from the responsibility of retaining study records, then custody of the records transfers to a person assuming responsibility. Sponsor will be notified in writing of new custodian by the investigative site.

15 USE OF INFORMATION AND PUBLICATION

Publications will follow guidelines in the LAANTERN Registry and the associated Publication Plan (CL10084). A committee will be formed for prioritization of PENSAR-specific publications. This study will be submitted for inclusion in the clinical trial study at: http://www.ClinicalTrials.gov.

16 REFERENCES

1. Bermudez CI, Jermakowicz WJ, Kolcun JPG, et al. Cognitive outcomes following laser interstitial therapy for mesiotemporal epilepsies. *Neurology: Clinical Practice*. Published online September 6, 2019:10.1212/CPJ.0000000000000728. doi:10.1212/CPJ.0000000000000728

2. Board of Directors. (2007). American Academy of Clinical Neuropsychology (AACN) Practice Guidelines for Neuropsychological Assessment and Consultation. The Clinical Neuropsychologist, 21(2), 209–231. https://doi.org/10.1080/13825580601025932

3. Drane DL, Loring DW, Voets NL, et al. Better object recognition and naming outcome with MRI-guided stereotactic laser amygdalohippocampotomy for temporal lobe epilepsy. *Epilepsia*. 2015;56(1):101-113. doi:10.1111/epi.12860