Clinical Protocol ALCMI-024

An Observational Study to Evaluate the Incidence of Clinically Suspicious Lambert-Eaton Myasthenic Syndrome (LEMS) in Subjects Diagnosed with Small Cell Lung Cancer (SCLC)

Issue Date(s): 12 June 2025

Issue Version V 1.0

IND Status: Exempt

Principal Investigator

Jacob M. Sands, MD

Thoracic Oncologist Dana-Farber Cancer Institute (DFCI)

Assistant Prof of Medicine, Harvard Medical School

450 Brookline Ave.

Boston, MA 02215

Phone: 617-632-6049

Email: Jacob_sands@dfci.harvard.edu

Co-Principal Investigator

Gilbert Youssef, MD

Neuro-Oncologist, Dana-Farber Cancer Institute (DFCI)

Instructor in Neurology, Harvard Medical School

450 Brookline Ave.

Boston, MA 02215

Phone: 817-632-6177

Email: Gilbert_youssef@dfci.harvard.edu

Study Manager

Allison M. Harper, PharmD

Director of Clinical Research

Addario Lung Cancer Medical Inst (ALCMI)

Phone: 704-996-6579

Email: aharper@alcmi.org

Sponsor

ADDARIO LUNG CANCER MEDICAL INSTITUTE (ALCMI)

1100 Industrial Rd, Suite 1

San Carlos, CA 94070

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Sponsor Statement

This protocol was subject to critical review and has been approved by the following persons:

Jacob M. Sands, MD
Thoracic Oncologist, Dana-Farber Cancer Institute (DFCI)

Date

Gilbert Youssef
Neuro-Oncologist, Dana-Farber Cancer Institute (DFCI)

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol ALCMI-024

An Observational Study to Evaluate the Incidence of Clinically Suspicious Lambert-Eaton Myasthenic Syndrome (LEMS) in Subjects Diagnosed with Small Cell Lung Cancer (SCLC)

Issue Date(s): 12 June 2025 Protocol Version: V1.0

Investigator Agreement

I have read the above-Mentioned protocol and am aware of my responsibilities as Investigator for this trial. As such, I agree to:

- Personally supervise the conduct of this trial
- Conduct the trial in accordance with International Conference on Harmonization E6 Good Clinical Practice (ICH GCP) Consolidated Guidance, applicable regulatory requirements, and the protocol.
- Comply with the procedures for data recording and reporting as required by the regulatory authorities and the Sponsor.
- Permit monitoring, auditing and inspection of trial records as required by ICH GCP.
- Retain the essential clinical trial documents as required by ICH GCP and the sponsor.

The information contained in this protocol is proprietary and provided to me in confidence, and may not be disclosed to any other party, in any form, without prior authorization from the sponsor, except to the extent necessary for conduct of the trial.

_____ _____

Investigator Signature Date

_____

Investigator Name (Print)

SYNOPSIS

Title of Study: An Observational Study to evaluate the incidence of clinically suspicious Lambert-Eaton Myasthenic Syndrome (LEMS) in subjects diagnosed with Small Cell Lung Cancer (SCLC)
Investigational sites: Up to 10 investigative sites; USA
Study Phase (if applicable): N/A observational study
Study Objectives and Endpoints: **Primary Objective(s):** • Evaluate the incidence of clinically suspicious LEMS diagnosis in Subjects diagnosed with Small Cell Lung Cancer **Secondary Objective(s):** • Correlate the occurrence of clinically suspicious LEMS neurologic symptoms with VGCC antibody positivity. • Evaluate the occurrence of clinically suspicious LEMS with Small Cell Lung Cancer. • Evaluate the occurrence of clinically suspicious LEMS with Lung Cancer treatments received. • Record the number of subjects enrolled with a prior LEMS diagnosis.
Study Rationale and Design: The incidence of LEMS associated with small cell lung cancer (SCLC) is described as about 3%, but population screening has not been evaluated. We hypothesize that the incidence of LEMS associated with SCLC is higher, and a screening test may help to better identify patients. We plan a multi-center testing of as many eligible patients as possible who present to clinic with small cell lung cancer. We will monitor testing every 3 months with documentation of any symptoms. Any workup will be done per standard of care.
Number of Subjects per Cohort: Up to 400 subjects with SCLC
Subject Population: Adult subjects meeting age of majority (AOM), with a diagnosis of SCLC will be enrolled.
Test Product: N/A Observational Study
Reference Product: N/A
Study Duration: Part A (est. 12 months): All subjects enrolled will have quarterly (Q 3 months) visits conducted during this initial 12-month period. At around month 12, enrollment and study visits will be suspended and an interim analysis for futility will be performed to determine if the study will progress into Part B. Part B: The duration and sample size for Part B will be determined from the Part A interim analysis.
Criteria for Evaluation: All enrolled subjects will be used for evaluation.
Statistical Methods: A descriptive analysis of all data collected will be carried out. • At 1 year (12 months) an interim analysis for futility will be conducted.

1 INTRODUCTION

1.1 Background

Lambert-Eaton Myasthenic Syndrome (LEMS) is a rare auto-immune presynaptic disorder of the neuromuscular junction (NMJ) associated with proximal muscle weakness, reduced or absent muscle stretch reflexes, and autonomic dysfunction **(PMID: 4330759)**. Up to 60% of cases occur in the setting of a paraneoplastic disorder, with small-cell lung cancer (SCLC) being the most common tumor type **(PMID: 21245427; 2838124; 15277653)**. Antibodies (Ab) against voltage-gated calcium channels (VGCC), particularly of the P/Q type, are identified in 85-90% of patients with LEMS **(PMID: 9668336; 7739683; 9094058)**. Antibodies to N-type and L-type VGCC have also been reported in 25-40% of LEMS, concurrently with the P/Q-type antibodies, where **(PMID: 8309586; 8583238)**, while few cases are seronegative.

Awareness of the clinical features, diagnostic evaluation, malignancy workup, and management of LEMS, as well as a high index of suspicion, are important for timely diagnosis and proper treatment. When LEMS is suspected or diagnosed, the evaluation of a primary malignancy, particularly SCLC, is warranted due to the strong association. A diagnosis of SCLC has been established within 1 year of LEMS diagnosis in 96% of patients **(PMID: 18779614)**. Treatment of the underlying malignancy may be the only intervention necessary to improve neurologic symptoms.

In the context of LEMS associated with SCLC, the median survival is approximately 18 months. Median survival in individuals with SCLC and LEMS is better than those with only SCLC (median survival of 17 vs 7 months). This longer survival was seen in both limited SCLC (median survival of 19 vs 12.1 months) and extensive SCLC (13 vs 4.9 months). Individuals with non–tumor–associated LEMS have a similar life expectancy to the general population.

1.2 Rationale

LEMS is a paraneoplastic syndrome that occurs in about 3% of individuals with small cell lung cancer, whereas the prevalence of VGCC antibodies at the time of SCLC diagnosis is estimated around 7-8% of patients (**PMID: 15904978; 19934775).** However, the frequency of neurologic symptoms has not been thoroughly evaluated, neither has longitudinal serial assessment of VGCC antibodies throughout the SCLC disease course.
This study aims at evaluating the incidence of LEMS in patients with SCLC at the time of their initial diagnosis, as well as at regular timepoints during their disease course.

1.3 Overall Benefit/Risk Assessment

This is an observational, non-treatment, non-interventional, non-randomized multi-center study in subjects who have been diagnosed with Small Cell Lung Cancer. No expected benefit or risk is anticipated for subjects participating in the study.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the incidence of clinically suspicious LEMS diagnosis in small cell lung cancer patients

2.2 Secondary Objective(s)

- To correlate the occurrence of clinically suspicious LEMS symptoms with VGCC antibody positivity
- To evaluate the occurrence of clinically suspicious LEMS with SCLC
- To evaluate the occurrence of clinically suspicious LEMS with Lung Cancer treatments received
- Record the number of subjects enrolled with a prior LEMS diagnosis

3 STUDY DESIGN AND EVALUATION

3.1 Study Design

This is a multi-center observational study in subjects with a diagnosis of small cell lung cancer. All eligible subjects enrolled will undergo a brief, symptom directed neurological evaluation and VGCC antibody testing (to be performed at a participating Quest laboratory). The results (positive/negative) of VGCC antibody testing will be documented as well as the receptor type P, Q or N.

These tests will be repeated quarterly (Q3 months) for the duration of the study.

If at any visit the subject is found to be BOTH neurologically suggestive of having LEMS and the VGCC Ab test is positive, then the subject is considered to be Clinically Suspicious of having LEMS. At any visit if a subject meets the criteria of Clinically Suspicious of LEMS. the end of study visit will be completed. Once the End of study visit is completed no further treatment information will be collected.

There will be an Investigator Intended Course of Action Form to record possible course(s) of action taken for all subjects who meet the definition of clinically suspicious LEMS (have positive VGCC antibody and suspicious neurologic symptoms). A confirmatory diagnosis of LEMS is by electrophysiologic studies, including repetitive nerve stimulation and/or single fiber electromyography, in patients with suspicious neurologic symptoms and positive VGCC antibodies. This observational (only) trial will not involve any medical course of action as an outcome to testing or participation in this trial, and no adjustments to the subject's existing treatment plan will result as an outcome to participation in this trial. Any treatment actions that

may be considered stemming from participation in this trial will not be considered as part of this observational study – and the intended course(s) of action only will be recorded in this trial. If a subject has been diagnosed with LEMS prior to enrollment in the study, the symptom directed neurological evaluation and VGCC Ab collection do not need to be completed. The enrollment visit and End of study visit will be completed once all diagnosis information has been collected. No further follow up will be needed for this subject.

This study is to be conducted in conformance with the International Conference on Harmonisation/Good Clinical Practices (ICH/GCP).

3.1.1 Duration of Study

Part A (est. 12 months): All subjects enrolled will have quarterly (Q 3 months) visits conducted during this initial 12-month period. At around month 12, enrollment and study visits will be suspended and an interim analysis for futility will be performed to determine if the study will progress into Part B.

Part B: The duration and sample size for Part B will be determined during from the Part A interim analysis.

If the interim analysis for Part A determines that Part B will not be conducted, then the study will be closed and all study close out procedures completed.

3.1.2 Screening / Enrollment

Potential subjects will be reviewed against the inclusion/exclusion criteria to determine eligibility. Small Cell Lung Cancer treatments received up to 30 days prior to enrollment will be collected.

Subjects will be enrolled once eligibility is confirmed.

3.1.3 Observation Period

The observation period begins at enrollment (day 0). Subjects will be evaluated with a symptom directed neurological evaluation and given an order for a VGCC Ab test to be completed at Quest Laboratory. Both the Symptom directed neurological evaluation and VGCC Ab test will be completed every 3 months while the trial remains open.

At each quarterly observation visit the following will be completed;

- Review of disease progression and current cancer therapy
- Complete the symptom directed neurological evaluation
- VGCC Ab test
    - Results of positive/negative and receptor subtype (P, Q, or N) will be documented.

At month 12 of Part A, enrollment and study visits will be suspended for an interim analysis.

3.1.4 Study Administration Structure

Protocol ALCMI-024 is sponsored by ALCMI. The administrative structure of the study is described in Table 4.1 Study Administrative Structure.

Table 4.1 Study Administrative Structure.

Group	Responsibility
Addario Lung Cancer Medical Institute (ALCMI)	Provide scientific direction for the study. Responsible for monitoring the progress of the study, data management, site monitoring, determining the need for modification of the protocol, publishing the results of the study.
Quest Diagnostic Laboratories	Collect, process and report the VGCC Ab test
REDCap Database	Electronic Data Capture for the study, Remote monitoring, and Datasets

3.2 Study Population

Adult subjects meeting age of majority with a diagnosis of SCLC will be evaluated for possible participation in the study. A goal of up to 400 SCLC subjects will be enrolled at approximately 10 investigational sites. It is anticipated that each investigational site will enroll approximately 40 SCLC subjects during Part A.

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be enrolled in the study.

3.3 Criteria for Evaluation

All data collected will be included in the data evaluation.

4 STATISTICICS

4.1 Sample Size Determination

The total target sample size will be up to 400 subjects. With an estimated 3% incidence of LEMS, which correlates with about 12 subjects to meet the definition of clinically suspicious of LEMS.

4.2 Data Set Descriptions

The “observation period” refers to all data collected once the subject is enrolled and has completed at minimum one Symptom directed neurological evaluation and/or one VGCC antibody test. The symptom directed neurological evaluation and VGCC Ab tests will not be completed for any subject enrolled with a prior LEMS diagnosis.

The data sets will consist of all data collected including all results of the symptom directed neurological evaluation and the VGCC antibody tests.

The Intended Course of Action determined by the investigators will also be collected for all subjects who have an incidence of clinically suspicious LEMS diagnosis.

4.3 Data Set Analyses

Descriptive analysis of all data collected will be carried out. The study will explore correlations between all variables – including demographics, medical history, symptom directed neurological evaluation, VGCC Ab results, VGCC Ab subtypes identified, number of subjects enrolled with a prior LEMS diagnosis, number of subjects with an incidence of clinically suspicious LEMS diagnosis, and Intended Course of Investigator Action forms. An incidence of clinically suspicious LEMS diagnosis is defined as neurologic symptoms suggestive of having LEMS and positive VGCC Ab.

4.3.1 Interim Analysis

At approximately 1 year (12 months) after enrollment start, there will be an interim analysis for futility. After review of the data there will be a determination if the study will close or if Part B of the study will be designed and conducted.

4.3.2 Safety Analyses

This study is an observational and blood sample collection study that does not involve treatment safety analyses.

5 Data Management

Every effort will be made to ensure that data management practices adhere to international standardization of the following data management procedures.

5.1 Database Design and Creation

The REDCap database system will be used for this study. This database will be designed to store the data as recorded in the source and will ensure a one-to-one mapping between the source and the electronic case report form (CRF) stored in the system.

5.2 Data Coding

Because this is a non-interventional, no treatment study, data coding is not required.

5.3 Data Entry and Verification

The data recorded on the protocol-unique source documents will be verified and entered into the REDCap trial database.

5.4 Data Transfer

Data transfers will be sent to Sponsor or their designee, electronically on a schedule and in a format mutually agreed upon by Sponsor or their designee, and the vendor responsible for the analysis of these data.

5.5 Database Lock

At around 12 months there will be a soft lock of the data for interim analysis. The interim analysis will determine if the study should be terminated or if Part B will be designed and conducted.

On completion of the entire trial (Part A and Part B if it is continued), after data entry is complete and the data has been pronounced clean, the database will be locked and final write access will be removed.

6 SUBJECT SELECTION AND DISCONTINUATION

6.1 Inclusion

Subjects must satisfy the following criteria before being enrolled into the study.

1) Adult men or women meeting Age of Majority (AOM) at the time of consent
2) Provide voluntary consent to participate in this study, documented via a signed informed Consent Form (ICF)
3) Any diagnosis of SCLC
4) Willing to provide clinical and medical information related to his/her cancer diagnoses to the study team as required
5) Willing to comply with the requirements of the study

6.2 Exclusion

A subject who meets any of the following exclusion criteria will be disqualified from participation in the study:

1) Has been diagnosed with non-tumor Lamber-Eaton Myasthenic syndrome (LEMS) > 1 year prior to the SCLC diagnosis.
2) Known existence of an uncontrolled intercurrent illness including, but not limited to, psychiatric illness or social situations that would impair compliance with study requirements

Note: Concurrent enrollment in other clinical trials is NOT exclusionary

6.3 Subject Discontinuation

6.3.1 Subject Discontinuation Criteria

Subject participation in the study may be prematurely discontinued for any of the following reasons:

- Withdrawal of informed consent (subject's decision and right to withdraw at any time for any reason);
- Any abnormality or intercurrent illness, which in the opinion of the investigator, indicates that continued participation in the trial is not in the best interest of the subject;
- Failure to comply with protocol requirements, evaluations, or other study parameters;
- Subjects who become prisoners or become involuntarily incarcerated;
- Termination of the study by Sponsor;
- Lost to follow-up.

6.3.2 Procedures for Discontinuation

The reason for withdrawal or discontinuation will be documented in the CRF and source documents. If a subject chooses to withdraw from the study the reason or event must be captured in the CRF and source documents on the End of Study CRF.

If a patient is lost to follow-up, a reasonable effort is required to contact the patient and perform the End of Study procedures. A reasonable effort is considered, at minimum, 3 phone attempts and/or 3 email attempts requesting patient to complete protocol requirements. The reason for withdrawal or discontinuation will be documented in the CRF and source documents.

6.3.3 Replacement of Subjects

Subjects who discontinue early will not be replaced in this study.

7 STUDY PROCEDURES AND OBSERVATIONS

7.1 Time and Events Schedule (Flow Chart)

Procedure	Screening*	Observation Period		
		Enrollment Visit*	Quarterly visit (Q 3 months)	End of study
Obtain Informed Consent	X			
Review Inclusion/Exclusion Criteria	X	X		
Relevant Medical History	X	X		
SCLC diagnosis and treatment	X	X		
Demographics (Age, sex, Race/Ethnicity)		X		
Review of disease progression and treatments			X	X
Symptom Directed Neurological Evaluation		X**	X	
VGCC Ab blood collection		X**	X	
Investigator Intended course of Action Form (for clinically suspicious LEMS only)				X
* The screening and enrollment visit can be completed on the same day. **If the subject has a prior LEMS diagnosis at enrollment do not complete these activities and also complete the End of study visit.				

7.2 Procedures by Visit

The investigator is responsible for adherence to the protocol. Prompt and complete reporting of all pertinent data is essential. In order to minimize variability of evaluations, it is preferred that the same individuals perform the same or similar evaluations within each subject in the study.

7.2.1 Screening Period* (Day -15 to Day 0)

- Obtain written informed consent
- Collect demographics (Age, sex, Race/Ethnicity)
- Collect SCLC cancer diagnosis and treatment (up to 30 days prior to enrollment)
- Collect relevant medical history, collect Medical History release form if needed
- Review Inclusion/Exclusion criteria
- Schedule Enrollment visit

7.2.2 Enrollment visit* (Day 0)

- Review inclusion/exclusion criteria
- Review SCLC cancer diagnosis and treatment
- Review of relevant medical history
- Symptom directed neurological evaluation

- Provide Quest lab order for VGCC Ab collection
- Schedule next observation visit in 3 months

7.2.3 Quarterly Observational visits (Q 3 months)

- Review SCLC disease progression and treatments
- Symptom directed neurological evaluation
- Provide Quest lab order for VGCC Ab collection
- Schedule next observation visit in 3 months

7.2.4 End of Study visit

This visit will be conducted at any time a subject has met the definition of clinically suspicious LEMS, when a subject has completed 12 months of observation, or study terminated by sponsor.

- Review SCLC disease progression and treatments
- Document reason for end of study
- Complete the Investigator Intended Course of Action form (Only complete for those subjects who met the definition of clinically suspicious LEMS).

*The screening and enrollment visit can occur on the same day.

7.3 Subject Assessments

7.3.1 *Demographics*

The demographics collected for this study will include subjects' date of birth, subject initials, age, sex at birth, race and ethnicity

7.3.2 *SCLC Cancer diagnosis and Treatment, relevant medical history*

The SCLC date of diagnosis and any cancer treatments will be collected. Relevant medical history to confirm inclusion/exclusion criteria will be collected.

If a subject has been diagnosed with LEMS prior to enrollment this will be documented in the subject's medical history including the date of LEMS diagnosis, date of EMG and findings, and any LEMS treatment given.

> **NOTE**: If a subject has been diagnosed with LEMS prior to enrollment the symptom directed neurological evaluation and VGCC Ab collection will not be completed. The enrollment visit and End of study visit will be completed once all diagnosis information has been collected. No further follow up will be needed for this subject.

7.3.3 *Symptom Directed Neurological Evaluation*

This evaluation will be administered by a delegated individual to make a determination of clinically suggestive or not clinically suggestive of having LEMS

If determined clinically suggestive of having LEMS the Investigator will complete the second part of the symptom evaluation to document the symptoms present.

If the subject's neurologic symptoms are suggestive of having LEMS the investigator will review to see if the VGCC antibody test was positive. If the subject is BOTH neurologically suggestive of having LEMS and the VGCC Ab test is positive, then the subject is considered as Clinically Suspicious of having LEMS and the end of study visit completed.

7.3.4 *VGCC Antibody Blood draw*

At each observation visit the subject will be provided an order for a VGCC antibody blood test, to be collected within 15 days of the visit, at the Quest Diagnostic Laboratory of their convenience. Quest will report the lab results to the Investigator. The results of positive or negative and any indicated subtype will be documented for the subject

If a positive result is found the Investigator will review if the subject has a clinically suggestive symptom directed neurological evaluation. If the subject is BOTH neurologically suggestive of having LEMS and the VGCC Ab test is positive, then the subject is considered as Clinically Suspicious of having LEMS and the end of study visit completed.

7.3.5 *Investigator Course of Action Form*

The investigator course of action will be completed to document what actions the investigator will take for each subject who is considered clinically suspicious of having LEMS.

At any visit if a subject is considered clinically suspicious of LEMS. the end of study visit will be completed. Once the End of study visit is completed no further treatment information will be collected.

8 INVESTIGATIONAL PRODUCT

Not Applicable as this is an observational study.

9 ADVERSE EVENT REPORTING IN CLINICAL TRIALS

Adverse events are not expected in this study, as the only change in patient care mandated by this protocol is an additional collection of blood. There may be a small risk of bruising or hematoma from the taking of the peripheral blood due to the needle stick, as well as a slight risk of fainting. However, any other evaluations (imaging, physical assessment, etc.) are considered to be standard of care in the evaluation of patients with lung cancer and would be performed as part of the standard of care clinical work-up, not for the purpose of this study.

10 QUALITY ASSURANCE

10.1 Compliance with Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, Sponsor or designee. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion;
- Sponsor;
- Regulatory Authority(ies), if required by local regulations.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Sponsor.

If an Amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the Amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

10.2 Monitoring for Protocol Compliance

Representatives of Sponsor must be allowed to visit all investigational site locations in person or remotely to periodically to assess the date, quality and study integrity. During these visits they will review study records in comparison with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by Sponsor internal auditors and government inspectors who must be allowed access to CRFs, source documents and other study files. Sponsor audit reports will be kept confidential.

Deviations to the protocol shall be recorded and reported to Sponsor and/or IRB as applicable.

THE INVESTIGATOR MUST NOTIFY SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO SPONSOR.

11 ETHICAL AND LEGAL CONSIDERATIONS

11.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, informed consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The IRB/IEC approval/favorable opinion should be obtained in writing, clearly identifying the trial, the documents reviewed, and the date of the review.

As appropriate, amendments to the above stated documents must also be submitted and receive approval/favorable opinion from the IRB/IEC prior to implementation at the investigational site. The IRB/IEC approval/favorable opinion should be obtained in writing, clearly identifying the trial, the documents reviewed, and the date of the review.

The Investigator or Sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure and/or product labeling, reports, updates and other information according to regulatory requirements or Institution procedures.

11.2 Informed Consent

Investigators must ensure that subjects or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate.

The following sections contain Sponsor procedures on obtaining informed consent from subjects or their legally acceptable representative prior to participating in a clinical trial. Procedures are described for all subjects, including those who are unable to give informed consent. The relevant procedures must be used whenever they are applicable.

11.2.1 Informed Consent Procedures

Preparation of the consent form is the responsibility of the Investigator and must include all elements required by ICH, GCP and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form must also include a statement that Sponsor and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the Investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The Investigator must provide the subject or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed

and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the trial.

11.2.2 Subjects Unable to Give Informed Consent

Patients must be able to provide consent to be included in this study.

11.2.2.1 Minors

Not applicable to this study.

11.2.2.2 Patients Experiencing Acute Events or Emergencies

Not applicable to this study.

11.2.2.3 Mentally Impaired or Incapacitated Subjects

Investigators should determine whether or not a mentally impaired or incapacitated subject is capable of giving informed consent and should sign a statement to that effect. If the subject is deemed mentally competent to give informed consent, the investigator should follow standard procedures. If the subject is deemed not to be mentally competent to give informed consent, a fully informed legal guardian or legally acceptable representative can be asked to give consent for, or on behalf of, the subject. All local laws, rules and regulations regarding informed consent of mentally impaired or incapacitated subjects must be followed.

11.2.2.4 Other Circumstances

Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infections disease) illness must not be enrolled in clinical trials.

In circumstances where a subject's only access to treatment is through enrollment in a clinical trial (e.g., for subjects in developing countries with limited resources or for subjects with no marketed treatment options), the investigator must take special care to explain the potential risks and benefits associated with the trial and ensure that the subject is giving informed consent.

Relatives of the investigator or the study staff must not be enrolled in the clinical trial.

11.2.3 Illiterate Subjects

If the subject or legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is appropriate independent witnesses. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the

subject or legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

11.2.4 Update of Informed Consent

The informed consent and any other information provided to subjects or the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The Investigator, or a personal designated by the Investigator should fully informed the subject or the subject's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

11.3 Confidentiality

11.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to Sponsor that information furnished to the investigator by Sponsor will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethical Review Committee, or similar or expert committee, affiliated institution, and employees only under appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in Section 12.4.

11.3.2 Confidentiality of Patient Records

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). By signing this protocol, the investigator agrees that Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify Case Report Form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during this process of verification, the subject will be identified by unique code only; full name/initials and other personal identifiers will be masked.

11.3.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information (e.g., name, hospital or clinic address, curriculum vitae) may be made part of a regulatory submission and may be transmitted (either in hard copy or electronically) to Sponsor for internal study management purposes or as required by individual regulatory agencies. Additionally, the investigator's name, hospital/clinic address/phone number may be included when reporting certain SAEs to regulatory agencies or to other investigators and stored in managed regulatory-controlled databases such as REDCap.

11.4 Publications and Other Rights

Manuscript(s) and abstract(s) will be prepared through cooperation between Sponsor and the study investigator(s).

11.4.1.1 Responsibilities

The principal investigator has the right to publish or publicly present the results of the study in accordance with this section of the protocol. In the event that the Protocol is part of a multi-center study, it is understood that it is the intent of Sponsor and the principal investigator to initially only publish or present the study results together with the other investigational sites, unless specific written permission is obtained in advance from Sponsor to publish separate results. Sponsor shall advise as to the implications of timing of any publication in the event clinical trials are still in progress at investigational sites other than that of the principal investigator's.

The principal investigator agrees not to publish or publicly present any interim results of the Study without prior written consent of Sponsor. The principal investigator further agrees to provide 45 days written notice to Sponsor prior to submission for publication or presentation to permit Sponsor to review copies of abstracts or manuscripts for publication (including, without limitation, slides and text of oral or other public presentations and text of any transmission through any electronic media, e.g., any computer access system such as the Internet, World Wide Web, etc.) which report any results of the Study. Sponsor shall have the right to review and comment on any presentation, which shall include editorial rights to:

(i) ensure that proprietary information is protected by the provisions contained in Section B below;
(ii) ensure the accuracy of the information contained in the presentation; and
(iii) ensure that the Public Presentation is fairly balanced as required by, and otherwise in compliance with, FDA Regulations.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality of Sponsor's confidential information, the principal investigator agrees to meet with Sponsor's representatives at the clinical investigational site or as otherwise agreed, prior to submission of presentation for publication, for the purpose of making good faith efforts to discuss and resolve any such issues or disagreement.

11.4.1.2 Patents

No publication or manuscript shall contain any trade secret information of Sponsor or any proprietary or confidential information of Sponsor and shall be confined to new discoveries and interpretations of scientific fact. If Sponsor believes there is patentable subject matter contained in any publication or manuscript submitted for review, Sponsor shall promptly identify such subject matter to principal investigator. If Sponsor requests and at Sponsor's expense, Principal Investigator shall use his/her best efforts to assist Sponsor to file a patent application covering such subject matter with the US Patent and Trademark Office or through the Patent Cooperation Treaty prior to any publication.

11.4.1.3 Right to Use

The principal investigator is granted the right to use the results of all work provided by principal investigator under this Protocol, including but not limited to, the results of tests and any raw data and statistical data generated for principal investigator's own teaching, research and publication purposes only. Principal investigator/institution agrees, on behalf of itself and its employees, officers, trustees, and agents, not to cause said results to be knowingly used for any commercial purpose whatsoever except as authorized by Sponsor in writing.

12 ADMINISTRATIVE

12.1 Records and Reports

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation. Data reported on the CRF, that are derived from source documents, must be consistent with the source documents or the discrepancies must be explained. Corrections to source documents must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be initialed and dated by the person making the correction and must not obscure the original entry. The source documents may further provide an explanation for the change, if necessary.

The eCRF must be completed within one week of subject visits. All requested information must be entered on the eCRF. If an item is not available or is not applicable, it must be documented as such; do not leave a space blank.

The Investigator will maintain a Site Signature and Delegation of Duties Log to document signatures and initials of all persons authorized to make entries and/or corrections on the eCRFs.

12.2 Records Retention

The investigator must maintain copies of all documents and records related to the conduct of the trial (such as investigational product disposition records, copies of CRFs (or electronic files), and source documents, etc.) for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by Sponsor.

If the Investigator wishes to relocate the records or is unable to retain them for the specified retention period, Sponsor must be contacted and notified in writing.

If the Investigator withdraws from the study (e.g., relocation, retirement) the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB). Sponsor must be notified in writing of any such transfer.

All trial documents shall be made available if required by relevant health authorities. The Investigator must contact Sponsor prior to destroying any records associated with the study.

12.3 Sponsor

Sponsor of this study is:

Addario Lung Cancer Medical Institute (ALCMI)
1100 Industrial Rd, Suite 1
San Carlos, CA 94070

12.4 Investigators, Investigational Sites and IRBs

Only investigators qualified by training and experience to perform a clinical investigation are selected. Sponsor or designee will contact and select all principal investigators (legally responsible party(ies) at each investigational site), who, in turn, will select their staff.

A list of active Investigator names, sub-investigator names, Institution names/ addresses and reviewing IRBs names/addresses is maintained by Sponsor, external to the protocol.

12.5 Central Organizations and/or Vendors

A list of names and addresses of organizations and/or vendors involved in patient management and associated testing and analysis where it affects the validity of the investigation is maintained by Sponsor, external to the protocol

13 LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
ALCMI	Addario Lung Cancer Medical Institute
AOM	Age of Majority
CDMS	Clinical Data Management System
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMG	Electromyography
ICH/GCP	International Conference on Harmonisation / Good Clinical Practices
HIPAA	The Health Insurance Portability and Accountability Act of 1996
Hx	History
IRB/IEC	Institutional Review Board / Independent Ethics Committee
kg	Kilogram
LEMS	Lambert-Eaton myasthenic syndrome
Q3m	Every three months
SCLC	Small Cell Lung Cancer
VGCC Ab	Voltage-gated calcium channel antibody test

14 REFERENCES

Jayarangaiah, A., Lui, F., & Kariyanna, P. T. (2023, October 23). *Lambert-Eaton Myasthenic Syndrome.* NCBI Bookshelf, National Library of Medicine, National Institutes of Health: StatPearls Publishing.

Lambert-Eaton Myasthenic Syndrome (LEMS) - Diseases . (2025). Retrieved from Muscular Dystorphy Association : https://www.mda.org/disease/lambert-eaton-myasthenic-syndrome

Matthew C. Varon, M., & Mazen M. Dimachkie, M. (2024). Diagnosis and Treatment of Lambert-Eaton Myasthenic Syndrome. *Autoimmune Neruomuscular Diseases*, 26-28, 47.

15 Appendices

15.1 Appendix 1: Quest Lab order

Quest Diagnostics™

ENTERPRISE ACCOUNTS, National Clinical Testing

FOR QUEST DIAGNOSTICS USE ONLY – QUESTIONS PLEASE CALL 1.866.226.8046

Account Number	97518573
Account Name	Catalyst Pharmaceuticals
Address	355 Alhambra Circle, Ste 801
City	Coral Gables
State	FL
Zip	33134

SPECIMENS MUST BE TESTED IN A QLS LABORATORY

Collection Date	
Collection Time	

Fax Results to:	

Ordering Physician and/or Payors		Physician Name	
UPIN		NPI	

CLIENT BILL ONLY NO PATIENT OR THIRD PARTY BILLING ON THIS ACCOUNT

Patient Information			
Patient Name (first, last, middle)			
Date of Birth	(MM/DD/YYYY)	Gender:	
Patient ID#			
Patient Phone			
Street Address			
City			
State		Zip	

	Order Code	Test Name		Order Code	Test Name
☐	34057	VGCC RIA [C]			
☐	93882	VGCC TYPE N AB			

15.2 Appendix 2: LEMS Symptom Directed Neurological Evaluation

SYMPTOM DIRECTED NEUROLOGICAL EVALUATION

Site #:		Subject #	024-
Visit:	☐Enrollment ☐3 month ☐6 month ☐9 month ☐12 month ☐ Other _____	Date of visit: (dd/mmm/yy)	

Paraneoplastic syndromes are clinical syndromes characterized by a recognizable grouping of signs and symptoms in patients with cancer. They affect about 1 in 10 patients with lung cancer, including small cell lung cancer (SCLC). Detecting them early can help improve patients' lives. The following symptoms are most commonly associated with LEMS

- recent muscle weakness on both sides of the body or a heaviness in legs or arms?
- recently experienced difficulty getting up from a chair?
- recently experienced dry eyes, dry mouth, or constipation?

Is the patient experiencing any of the signs and symptoms of LEMS?

☐ YES Continue to the next 2 questions

☐ NO This survey is complete, schedule the subject for the next visit

If this subject was **not** participating in this study, based on the review of the subject symptoms would you have normally ordered a VGCC Ab test?

☐ YES

☐ NO

Do you consider this subject's neurologic symptoms **suggestive of having LEMS**?

☐ YES Complete page 2 of this survey to describe the symptoms observed.

☐ NO This survey is complete, schedule the subject for the next visit

Signature of person completing this form: _____

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SYMPTOM DIRECTED NEUROLOGICAL EVALUATION

Site #:		Subject #	024-
Visit:	☐Enrollment ☐3 month ☐6 month ☐9 month ☐12 month ☐ Other _____	Date of visit: (dd/mmm/yy)	

Indicate the symptoms the subject has which are suggestive of having LEMS.
(check all that apply)

- ☐ Dry eyes, drooping eyelids, and/or blurred vision
- ☐ Proximal Arm (muscle weakness), difficulty raising arms or lifting objects
- ☐ Proximal Leg (muscle weakness), upper leg weakness or lower leg weakness
- ☐ Absent deep tendon reflexes
- ☐ Distal leg (muscle weakness)
- ☐ Post Exercise facilitation
- ☐ Dry Mouth, difficulty swallowing
- ☐ Orthostatic Hypotension, dizziness upon standing
- ☐ Constipation
- ☐ Impotence, erectile dysfunction

In some patients, a waddling gait may be indicative of LEMS
(check the box that best describes their gait)

- ☐ Patient walks with a waddling gait
- ☐ Patient does not walk with a waddling gait

Use the QR code to watch a classic example of "LEMS gait

Document any other symptoms noted for this subject.

If the subject's neurological symptoms are suggestive of **having LEMS**, review along with the VGCC Ab results.

☐If the subject is **BOTH** neurologically suggestive of having LEMS and the VGCC Ab test is positive, then the subject is considered as **Clinically Suspicious of a LEMS Diagnosis** as defined in the protocol. The subject has met the criteria to complete the study. Complete the End of Study visit for the subject including the Investigator Course of Action Form.

☐If the VGCC antibody test is **negative**, the subject does not meet the criteria to complete the study. Schedule the subject for the next study visit in 3 months.

☐ End of study ☐ Next visit scheduled

Signature of person completing this form: _____

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15.3 Appendix 3: Investigator Course of Action Form

Investigator Course of Action Form

Site #:		Subject #	024-
Visit:	☐Enrollment ☐3 month ☐6 month ☐9 month ☐12 month ☐ Other _____	Date of visit: (dd/mmm/yy)	

Complete this form at the End of Study visit.

This subject has met the criteria to be considered clinically suspicious of LEMS.

Please indicate what course of action best describes what will be done for this subject.

Check all that apply

- ☐ I will continue to follow the subject for symptoms of LEMS
- ☐ I will repeat the VGCC Antibody test
- ☐ I will refer the subject to Neurology for further evaluation
- ☐ I will continue to follow the subject without pursuing LEMS diagnosis
- ☐ Other: _____

Signature of Investigator: Date (dd/mmm/yy): _____

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