

CLINICAL STUDY PROTOCOL

Study Title: A Phase 3, Double-blind, Placebo-controlled, Randomized, Parallel-Group Study to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with Lambert-Eaton Myasthenic Syndrome (LEMS)

Protocol Number: LMS-003

Investigational Product: Amifampridine phosphate (3,4-diaminopyridine phosphate)

IND/EUDRACT Number: 106263 / 2010-021850-20

Indication: Lambert-Eaton Myasthenic Syndrome (LEMS)

Sponsor: Catalyst Pharmaceuticals, Inc.

Development Phase: Phase 3

Medical Officer: Gary Ingenito, MD, PhD

Study Design: Double-blind, Placebo-controlled, Randomized, Parallel-Group

Dose: 30-80 mg total daily dose or placebo equivalent

Patient Population: Patients with LEMS

Date of Protocol: 2 September 2016

Date of Amendment 1: 18 September 2016

Date of Amendment 2: 27 April 2017

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May not be divulged, published, or otherwise disclosed to others without prior written approval from Catalyst Pharmaceuticals, Inc.

This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents

1. PROCEDURES IN CASE OF AN EMERGENCY

Table 1. Emergency Contact Information

Role in Study	Name	Contact Information
Medical Monitor	Gary Ingenito, MD, PhD, Chief Medical Officer	Catalyst Pharmaceuticals, Inc. 355 Alhambra Circle, Suite 1250 Coral Gables, FL 33134 Tel: +1 305-420-3200, ext. 123 Email: gingenito@catalystpharma.com
Clinical Project Lead	Adriana Manari Clinical Trial Manager	Catalyst Pharmaceuticals, Inc. 355 Alhambra Circle, Suite 1250 Coral Gables, FL 33134 Tel: +1 305-420-3200, ext. 117 Email: amanari@catalystpharma.com
SAE Reporting	Reported within 24 hours	24-hour safety hotline: 305-420-3233 To ensure notification in real time, also email reports to: jrubine@catalystpharma.com and gingenito@catalystpharma.com

2 SYNOPSIS

NAME OF COMPANY:

Catalyst Pharmaceuticals, Inc.
 355 Alhambra Circle, Suite 1250
 Coral Gables, FL 33134

NAME OF INVESTIGATIONAL PRODUCT:

Active ingredients: amifampridine phosphate (3,4-diaminopyridine phosphate)

TITLE OF STUDY:

A Phase 3, Double-blind, Placebo-controlled, Randomized, Parallel-Group Study to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with Lambert Eaton Myasthenic Syndrome (LEMS).

PROTOCOL NUMBER:

LMS-003

STUDY SITE:

Up to 3 centers in the United States

PHASE OF DEVELOPMENT:

Phase 3

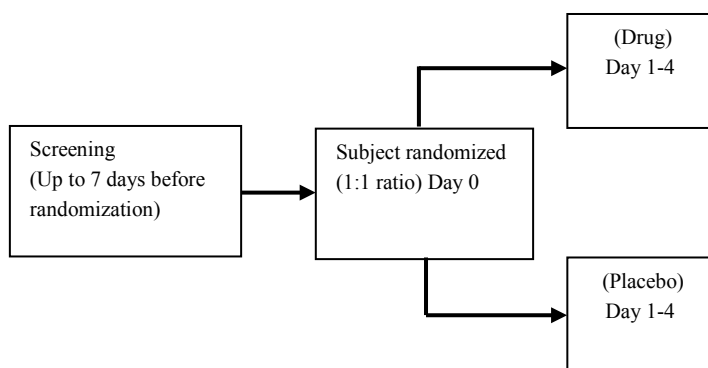
OBJECTIVES:

- Primary:
 - To assess the clinical efficacy of amifampridine phosphate compared with placebo in adults with LEMS, based on change of the co-primary endpoints QMG Score and Subject Global Improvement (SGI)
- Secondary:
 - Clinical Global Impression of Improvement (CGI-I)
- Exploratory:
 - Greater than 20% increase in the average time of 3 repetitions for Timed Up and Go test (3TUG)
 - Patient rating on change of most bothersome symptom for them

STUDY DESIGN AND PLAN:

This randomized (1:1), double-blind, placebo-controlled, parallel-group study is designed to evaluate the efficacy and safety of amifampridine phosphate in patients diagnosed with LEMS. Patients will have been receiving amifampridine phosphate, after which blinded treatment effect will be assessed for continuation or cessation of drug. The study is planned to include approximately 28 male and female patients. The planned duration of participation for each patient is 5 days (Day 0 through Day 4), excluding the screening period, which can last up to 7 days.

Those patients satisfying all inclusion and exclusion criteria will be randomized to a Treatment Group. Amifampridine phosphate (at the patient's optimal dose) or placebo will be dispensed by the site pharmacist, according to the randomization schedule, to begin with the next dose after all Day 0 assessments are completed and continued for 4 days. After completion of the study, patients will be eligible for expanded access treatment program with open-label amifampridine phosphate.



Screening

Patients receiving amifampridine phosphate treatment for LEMS, and meeting the inclusion and exclusion criteria are eligible to participate in this study. They can be randomized if on a stable dose and frequency of amifampridine phosphate for at least 1 week before being randomized.

Treatment (Days 1-4) (+1 day)

Patients will be randomized (1:1 ratio) on the last day of the screening period (Day 0) to either amifampridine phosphate or placebo. Beginning with the next dose after all Day 0 assessments are completed, the patient will take, under double-blind conditions, either amifampridine phosphate tablets or placebo tablets through Day 4, with a clinic visit on the last day (Day 4) for assessments ([Table 3](#)). Any unused portion of dispensed drug will be returned.

During all phases of the study, safety and efficacy assessments will be made as detailed in the Schedule of Assessments in [Table 3](#).

NUMBER OF PATIENTS PLANNED:

Approximately 28 patients to enroll in the study.

CRITERIA FOR INCLUSION AND EXCLUSION:

Individuals eligible to participate in this study must meet all of the following inclusion criteria:

1. Male or female ≥ 18 years of age with LEMS and currently receiving a stable dose of amifampridine phosphate for at least 7 days.
2. Diagnosis of LEMS by antibody testing or EMG.
3. Completion of anti-cancer treatment at least 3 months (90 days) prior to Screening.
4. If receiving peripherally acting cholinesterase inhibitors (e.g. pyridostigmine), a stable dose of cholinesterase inhibitors is required for at least 7 days prior to randomization and throughout the study.
5. If receiving permitted oral immunosuppressants (prednisone or other corticosteroid), a stable dose is required for at least 30 days prior to randomization and throughout the study.
6. Female patients of childbearing potential must practice an effective, reliable contraceptive regimen during the study.
7. Able to perform all study procedures and assessments.
8. Willing and able to travel to study site and attend all clinic study visits.
9. Willing and able to provide written informed consent.

Individuals who meet any of the following exclusion criteria are not eligible to participate in the study:

1. Clinically significant long QTc interval on ECG in previous 12 months.
2. Seizure disorder.
3. Active brain metastases.
4. Unable to ambulate.
5. Pregnant or lactating females.
6. Any other condition which, in the opinion of the Investigator, might interfere with the patient's participation in the study or confound the assessment of the patient.
7. Patients who cannot discontinue immunomodulatory treatment (e.g. mycophenolate, azathioprine, cyclosporine) within 3 weeks before screening.

INVESTIGATIONAL PRODUCT(S), DOSE, ROUTE, AND REGIMEN:

The investigational product (IP) is amifampridine phosphate tablets 10 mg, and it will be provided in round, white-scored tablets, containing amifampridine phosphate formulated to be the equivalent of 10 mg amifampridine base per tablet. The total daily dose will be individually determined by the Investigator, within the bounds of a total daily dose of up to 80 mg, divided into doses taken 3 to 4 times per day as prescribed by the Investigator, based on optimal neuromuscular benefit.

Amifampridine phosphate tablets are to be taken orally by mouth.

The investigational product, and matching placebo, will be provided by Catalyst Pharmaceuticals, Inc., 355 Alhambra Circle, Suite 1250, Coral Gables, Florida, 33134, United States.

REFERENCE THERAPY, DOSE, ROUTE, AND REGIMEN:

The reference therapy is a placebo, provided as tablets indistinguishable from amifampridine tablets. The placebo will be administered consistent with the dose and dose regimen of the investigational product (amifampridine phosphate).

CRITERIA FOR EVALUATION:**Safety:**

Safety will be assessed by the incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs). Vital signs, physical examination, and concomitant medications will also be evaluated.

Efficacy:

- Primary:
 - To assess the clinical efficacy of amifampridine phosphate compared with placebo in individuals with LEMS, based on change of the co-primary endpoints QMG Score and Subject Global Improvement (SGI).
- Secondary:
 - Clinical Global Impression of Improvement (CGI-I)
- Exploratory:
 - Greater than 20% increase in the average time of 3 repetitions for Timed Up and Go test (3TUG)
 - Patient rating on change of most bothersome symptom for them.

STATISTICAL METHODS:**Sample Size Determination**

For Change From Baseline in QMG Scores, a between-treatment difference of -3.5 and a standard deviation at most 3, a sample size of 24 patients will provide power of at least 80% for a 0.05 level test. Similarly, for Change From Baseline in SGI Scores, a between-treatment difference of -2.1 and a standard deviation at most 2, a sample size of 26 patients will provide power of 80% for a 0.05 level test. Thus a total sample size of 26 patients, equally randomized to the two treatments, will provide power of at least 80% for each of the two co-primary endpoints.

Safety Analysis

Safety analyses will be conducted on the safety population (i.e. all patients who receive at least 1 dose of amifampridine or placebo). The safety analysis will be descriptive and will be presented on using observed data only.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Only

treatment-emergent AEs (TEAEs) will be included in the safety analysis. The incidence of TEAEs will be summarized by system organ class, preferred term, relationship to treatment, and severity by treatment.

All other safety measures including vital signs, physical examination, and concomitant medications data will also be summarized.

Efficacy Analysis

Efficacy analysis will be conducted on 2 datasets:

- Full Analysis Set (FAS): This population consists of all randomized patients who receive at least 1 dose of IP (amifampridine or placebo) and have at least one post-treatment efficacy assessment.
- Per Protocol (PP): This population is a subset of the FAS population, excluding patients with major protocol deviations. The PP population will include all patients who:
 - Have no major protocol deviations or inclusion/exclusion criteria deviations that might potentially affect efficacy, and
 - Patients who took at least 80% of the required treatment doses and remained enrolled for at least 4 days.

Evaluations obtained at the time of discontinuation will be included in the analyses. Patients who discontinue with no post-randomization data will be excluded from all efficacy analyses but will be included in the safety analyses.

For each efficacy variable with a corresponding assessment at Baseline, Change From Baseline (CFB) will be computed as the post-treatment result minus the Baseline result. The post-treatment result will be the result obtained on Day 4, unless the patient discontinued treatment early, in which case the post-treatment result may be obtained at an earlier time point. For statistical test, two-sided P values <0.05 will be considered as statistically significant.

Summary statistics for QMG score and the corresponding CFB will be presented by treatment. The analysis of CFB for Total QMG Score is a coprimary efficacy endpoint and analysis will be performed by fitting a fixed effects linear model to the data with CFB as the response. The model will include terms for treatment and QMG at Baseline. A test comparing the least squares (LS) means will be conducted to evaluate the treatment effect.

The raw scores and CFB for each item of QMG will be summarized by treatment. Between-treatment comparisons with respect to CFB for Right arm outstretched, Left arm outstretched, Right leg outstretched, and Left leg outstretched will be performed using a fixed effects linear model with terms for treatment and QMG at Baseline.

Summary statistics for SGI score and the corresponding CFB will be presented by treatment. The analysis of CFB for SGI is a coprimary efficacy endpoint and analysis will be performed by fitting a fixed effects linear model to the data with CFB as the response. The model will include terms for treatment and SGI at Baseline. A test comparing the LS means will be conducted to evaluate the treatment effect.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

3,4-DAP	3,4-diaminopyridine
ACh	acetylcholine
AChR	acetylcholine receptor
ADL	Activities of Daily Living
ADME	absorption, distribution, metabolism, and excretion
AE(s)	adverse event(s)
AIN	adult idiopathic nystagmus
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
ANS	autonomic nervous system
AST	aspartate aminotransferase
ATU	Autorisations Temporaires d'Utilisation Normative
AUC	area under the plasma concentration-time curve
AUC _{0-∞}	area under the plasma concentration-time curve from time 0 to infinity
Ca ⁺	calcium ion
CI	confidence interval
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
C _{max}	peak plasma concentration
CMG	congenital myasthenia gravis
CMS	congenital myasthenic syndromes
CNS	central nervous system
CRA(s)	clinical research associate(s)
CRF	case report form (paper or electronic)
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DBP	diastolic blood pressure
EC	European Commission
ECG(s)	electrocardiogram(s)
EFNS	European Federation of Neurological Societies

EMG	Electromyogram
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
hERG	human Ether-à-go-go Related Gene
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IVIG	intravenous immunoglobulin G
JMS	juvenile myasthenia gravis
K ⁺	potassium ion
kg	kilogram
LEMS	Lambert-Eaton myasthenic syndrome
LRP4	Low Density Lipoprotein Receptor-Related Protein 4
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MFM	Motor Function Measure
MG	Myasthenia Gravis
MI	myocardial infarction
mmHg	millimeters of mercury
MS	multiple sclerosis
NAT	N-acetyl transferase
ng/mL	nanograms per milliliter
NMJ	neuromuscular junction
PE	plasma exchange
Pgp	P-glycoprotein
PK	pharmacokinetic

PP	per protocol
QID	four times daily
QMG	quantitative myasthenia gravis
QTc	QT wave corrected for heart rate
REB	research ethics board
SAE(s)	serious adverse event(s)
SBP	systolic blood pressure
SGI	subject global impression
SOPs	standard operating procedures
SFEMG	single fiber electromyogram
$t_{1/2}$	elimination half-life
TEAE(s)	treatment emergent adverse event(s)
TID	three times daily
TK	toxicokinetic
T_{max}	time to reach maximum plasma concentration
TPE	Therapeutic Plasma Exchange
US	United States

Definition of Terms:

Investigational Product (IP):

“A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use” (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 [ICH E6]). The terms “IP” and “study drug” may be used interchangeably in the protocol.

4 ETHICS**4.1 Institutional Review Board / Independent Ethics Committee**

The Investigator will provide the institutional review board (IRB), independent ethics committee (IEC), or research ethics board (REB) with all appropriate material, including the protocol, Investigator’s Brochure or Package Insert, the Informed Consent Form (ICF)

including compensation procedures, and any other written information provided to the patients, including all ICFs translated to a language other than the native language of the clinical site. The study will not be initiated and Investigational Product (IP) supplies will not be shipped to the site until appropriate documents from the IRB/IEC/REB confirming approval of the protocol, and the ICF are obtained by the Investigator. The approval document should refer to the study by protocol title and Catalyst protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. Catalyst will ensure that the appropriate reports on the progress of the study are made to the IRB/IEC/REB and Catalyst by the Investigator in accordance with applicable guidance documents and governmental regulations.

4.2 Ethical Conduct of Study

This study will be conducted in accordance with the following:

- US Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable;
- ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (ICH E6); and
- The ethical principles established by the Declaration of Helsinki.

4.3 Patient Information and Informed Consent

A properly written and executed ICF, in accordance with the Declaration of Helsinki, ICH E6 (Section 4.8), 21 CFR Part 50 that address clinical research studies, and other applicable local regulations, will be obtained for each patient before entering the patient into the study. The Investigator will prepare the ICF and provide the documents to Catalyst, or designee, for review. The IRB/IEC/REB must approve the documents before their implementation. A copy of the approved ICF, and if applicable, a copy of the approved patient information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by Catalyst or designee before any study-specific procedures being performed.

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with Catalyst, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each patient. If permission to use protected health

information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the patient and the patient will be removed from the study.

The Investigator will provide copies of the signed ICF and HIPAA authorization (or similar permission form) to each patient and will maintain the original in the record file of the patient.

5 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Before beginning the study, the Investigator at each site must provide to Catalyst or designee, a fully executed and signed US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-investigators listed on the Form FDA 1572 who will be directly involved in the treatment or evaluation of patients in this study.

The study will be administered by and monitored by employees or representatives of Catalyst. The responsible Medical Officer is:

Gary Ingenito, MD, PhD
Chief Medical Officer
Catalyst Pharmaceuticals, Inc.
Tel: +1 305-420-3200, ext. 123
Email: gingenito@catalystpharma.com

Clinical research associates (CRAs) or trained designees will monitor each site on a periodic basis and perform verification of source documentation for a representative sample of patients as well as other required review processes. Catalyst (or designee) will be responsible for the timely reporting of serious adverse events (SAEs) to appropriate regulatory authorities as required.

Laboratory evaluations, if required, will be performed at both local laboratories and central laboratories. Additional details will be provided in the LMS-003 Study Reference Manual. Urine samples for evaluation of dosing compliance and blood specimen for patients who opt for 'liquid biopsy' cancer screening will be sent to central laboratories.

6 INTRODUCTION

A comprehensive review of amifampridine phosphate is contained in the [Firdapse® Investigator's Brochure](#) supplied by Catalyst (February, 2015). Investigators are to review the document before initiating this study.

6.1 Disease Background

Lambert-Eaton Myasthenic Syndrome (LEMS) is a very rare autoimmune disease with the primary symptom of proximal muscle weakness. Muscle weakness resulting from LEMS is caused by auto-antibodies directed against type P/Q voltage-gated calcium channels (VGCCs) located on the pre-synaptic member of the neuromuscular junction (NMJ) ([Motomura, 1997](#)). Auto-antibodies inhibit the entry of calcium into the nerve, impairing the release of acetylcholine from nerve terminals into the synapse, resulting in a loss of neuromuscular transmission ([Augustine, 1990](#); [Lambert, 1956](#); [Verschuuren, 2006](#)).

Although the true prevalence of LEMS is uncertain, it has been estimated that this disease affects approximately 1 – 9 out of 100,000 of the general population ([Sanders, 2003](#)). Available literature suggests that approximately 50% to 55% of patients have a paraneoplastic form of LEMS, mainly small cell lung cancer (SCLC) ([Verschuuren, 2006](#); [Wirtz, 2002a](#)). In a large clinical study that included 50 consecutive patients with LEMS, SCLC was present in 84% of patients with cancer ([O'Neill, 1988](#)). The prevalence of LEMS in patients with SCLC is estimated to be approximately 3% ([Payne, 2010](#)). In approximately 90% of patients with the paraneoplastic form of LEMS, a tumor was detected within 2 years following the diagnosis of LEMS ([Verschuuren, 2006](#); [Elias, 2010](#)).

Clinically, LEMS is characterized by proximal muscle weakness usually greater in the hip than shoulder girdle muscles, fatigability, muscle aches, and autonomic dysfunction (e.g. impotence, dry mouth, constipation) ([Lambert, 1956](#); [Verschuuren, 2006](#)). Other symptoms may include paresthesias, diplopia, and orthostatic hypotension ([Wirtz, 2002b](#)). The characteristic proximal muscle weakness can compromise the most basic tasks such as walking and climbing stairs. The symptoms of impaired neuromuscular transmission typically present after age of 40, with a peak incidence between 50 and 70 years ([Wirtz, 2002b](#); [O'Neill, 1988](#)). The onset of symptoms is usually gradual and insidious, taking place over several weeks to many months or even years. In rare cases, weakness of the respiratory muscles can lead to a life-threatening respiratory crisis that necessitates artificial ventilation ([O'Neill, 1988](#); [Maddison, 1999](#)). There have also been isolated reports of patients presenting with acute

respiratory failure as the primary symptom of LEMS ([Verschuuren, 2006](#); [Elias, 2010](#); [Vedeler, 2006](#)). In LEMS, the gradual onset of hip girdle weakness is typically an early symptom with less dramatic shoulder girdle weakness. Clinical features that present later in LEMS include muscle weakness that worsens with prolonged exercise, respiratory muscle weakness, diplopia, and dry mouth ([Seneviratne, 1999](#)).

The diagnosis of LEMS is typically based on clinical findings and the presence of antibodies to VGCC and electrodiagnostic studies. The VGCC radioimmunoassay detects the ability of patient's serum to induce immunoglobulin G (IgG)-calcium complex precipitates after exposure to solubilized calcium channels. As discussed above, antibodies against the P/Q-type VGCC are present in approximately 85% to 95% of patients with LEMS.

In addition, a characteristic electrophysiologic pattern associated with LEMS may support the diagnosis of a presynaptic NMJ disorder. The compound muscle action potential (CMAP) amplitude in a resting muscle in patients with LEMS is usually significantly reduced. Following high frequency (10-50 Hertz [Hz]) repetitive nerve stimulation (RNS), there is a significant increment ($> 100\%$) with a marked increase in the CMAP amplitude ([Weinberg, 2010](#)). An increase in the CMAP amplitude $> 100\%$ after high frequency stimulation or exercise is considered diagnostic of a presynaptic NMJ disorder. In addition, the muscle action potentials observed in patients with LEMS are often unstable on electromyography (EMG) needle examination and the single fiber EMG typically has significant jitter and transmission blocking that is characteristically improved at higher firing rates ([Trontelj, 1991](#); [Chaudhry, 1991](#)).

Management of patients with LEMS can be classified into 3 main categories, each targeting different aspects of the pathogenesis of the disease: 1) anti-tumor treatment (e.g. chemotherapy, multikinase inhibitors) in paraneoplastic LEMS, 2) immunologic treatments (e.g. intravenous immunoglobulin (IVIG), plasma exchange, immunoadsorption, prednisone, azathioprine) to suppress anti-VGCC antibodies; and 3) symptomatic treatment (e.g. pyridostigmine, amifampridine) acting at the NMJ ([Verschuuren, 2006](#)).

The most common cancer accompanying LEMS is SCLC, but lymphoproliferative disorders such as Hodgkins Disease, carcinoid or malignant thymoma may also occur. Although there are no large clinical studies addressing immunotherapy, standard approaches have been

developed from small clinical trials, case reports, and clinical experience in the more frequent NMJ autoimmune disorder, myasthenia gravis (MG). Intravenous immunoglobulin has been demonstrated to increase muscular strength in small clinical trials and can be a maintenance therapy if administered approximately monthly. Prednisone is typically started at approximately 1 mg/kg/day, maintained at that dosage until there is clinical evidence of improvement, and then slowly tapered. The most frequently used steroid-sparing oral immunosuppressants are azathioprine or mycophenolate. Although evidence is limited, cyclosporine and plasmapheresis are sometimes used in refractory patients. As in other autoimmune disorders, immunologic agents are often used in combination. Although most experts recommend using similar immunotherapy in paraneoplastic and autoimmune LEMS, some physicians are reluctant to immunosuppress patients with malignancy ([Weinberg, 2010](#)).

Symptomatic treatment is integral to the management of LEMS, and typically is started prior to immunotherapy. The first available symptomatic treatment was guanidine, which acts by increasing transmitter release from presynaptic terminals. However, a small therapeutic window with side effects of marrow suppression and nephrotoxicity limited its use. Cholinesterase inhibitors alone (e.g. pyridostigmine) confer little benefit in LEMS ([Wirtz, 2009](#)), although are sometimes used in combination with guanidine. Aminopyridines, such as amifampridine, are first-line symptomatic therapy for patients with LEMS ([Skeie, 2006](#); [Skeie, 2010](#); [Lindquist, 2011](#)).

6.2 Amifampridine

Amifampridine (3,4-DAP) is a non-specific voltage-dependent potassium (K^+) channel blocker used to treat LEMS. Its blockade of K^+ channels causes depolarization of the presynaptic membrane and slows down or inhibits the repolarization phase of an action potential. Prolongation of the action potential duration increased opening of pre-synaptic slow voltage-dependent calcium (Ca^{2+}) channels, increasing Ca^{2+} influx and consequent increase in synaptic vesicle exocytosis (quantal content) with each depolarization event, thus releasing an increased level of ACh into the synaptic cleft ([Maddison, 1998a](#); [Maddison, 1998b](#)). The influx of ACh into the presynaptic cleft enhances neuromuscular transmission, providing improved muscle function.

Over the last 25 years, a considerable amount of clinical experience with amifampridine has been gained, which provides a strong body of evidence for its efficacy and safety in the

treatment of patients with neurologic disorders, including MG, CMS, LEMS, multiple sclerosis (MS), downbeat nystagmus, and amyotrophic lateral sclerosis (ALS).

Amifampridine has been recommended as first-line symptomatic treatment for LEMS by the European Federation of Neurological Societies (EFNS) ([Skeie, 2006](#); [Skeie, 2010](#); [Lindquist, 2011](#)) and amifampridine tablets 10 mg (as amifampridine phosphate) (Firdapse® Tablets) is marketed for the treatment of LEMS in the European Union (including Norway and Iceland), Israel, and Switzerland. The collective body of data indicates that amifampridine/amifampridine phosphate is well tolerated up to and including 80 mg/day (Firdapse Investigator Brochure, February 2015).

6.3 Nonclinical Studies

An extensive nonclinical program assessed the safety and absorption, distribution, metabolism, and excretion (ADME) and pharmacokinetic (PK) properties of amifampridine, including:

- Five safety pharmacology studies in central nervous system (rat), respiratory (rat), and cardiovascular (telemeterized dogs, *in vitro* human Ether-à-go-go Related Gene (hERG) and rabbit Purkinje fiber)
- Pharmacokinetics and mass balance in rat and dog
- *In vitro* metabolism in human and animal hepatocytes
- Human hepatic cytochrome P450 (CYP450) inhibition and induction
- Human P-glycoprotein (Pgp) interaction
- Single dose toxicity and toxicokinetic (TK) studies in mouse, rat, and beagle dog
- Repeat dose toxicity and toxicokinetic in rat (28-day and 13-week) and dog (28-day and 9-month)
- Reproductive and developmental toxicity in rat and rabbit
- Six *in vitro* and *in vivo* genotoxicity studies
- Carcinogenicity study (104 weeks) in rats

Safety factors based on data from the 4-week toxicity/TK studies in rat and dog, the 13-week toxicity/TK study in rats along with a PK study in fasted rats are presented in [Table 2](#). Peak plasma concentration (C_{\max}) values were used in calculating the exposure-based safety factors as the central nervous system (CNS) and autonomic nervous system (ANS) effects are correlated to plasma concentration levels. C_{\max} data from the bioavailability/bioequivalence study in healthy volunteers were used to compare with animal C_{\max} data. Human safety factors calculated using mean C_{\max} from a PK study in fasted rats are 2.8 (male) and 7.8 (female). The

safety factor based on average C_{max} in male and female dog versus human is 1.2 and 1.1, respectively.

Table 2. Body Surface Area and Exposure-Based Safety Factors

Species	NOAEL (mg/kg/day)	Clinical dose ^a (mg/kg/day)	C_{max} (ng/mL) (M/F)	Body Surface Area-Based Safety Factor	C_{max} -Based Safety Factor (M/F)
Rat PK study ^b	NA	NA	179/503	NA	2.8/7.8
Rat 4-Week ^c	24	NA	51.9/80.2	3.0	0.8/1.2
Rat 13-week ^d	22.5	NA	88.5/223	NA	NA
Dog 4-week ^e	1.9	NA	74.9/72.3	0.8	1.2/1.1
Human ^f	NA	1.3	64.8	NA	NA

C_{max} , peak plasma concentration; F, female; M, male; NA, not available; NOAEL, no observed adverse effect level; TID, 3 times daily

^a Based on a 60-kg human and a total daily dose of 80 mg/kg or 20 mg amifampridine phosphate, TID in order to calculate body surface area and C_{max} based safety factors, respectively.

^b Dose was 24 mg/kg/day, TID in fasted rats; based on fasted first dose.

^c Based on Day 27 of the first 4-week study in rat.

^d Based on Day 92 after third daily dose.

^e Based on Day 0 of the first 4-week study in dog.

^f Bioavailability/Bioequivalent clinical study in fasted healthy volunteers.

The main nonclinical findings of CNS and ANS effects and histologic changes in muscle tissues after administration of amifampridine are in accordance with the mechanism of action. No new treatment-related findings in the nonclinical program have been observed that would limit the use of amifampridine at the planned clinical maximum daily oral dose of 80 mg in this study involving patients with LEMS.

6.3.1 Carcinogenicity Study

A study of amifampridine phosphate consumption equivalent to 8, 25, or 55 mg/kg/day via dietary admixture in male and female Sprague Dawley rats showed no increased early mortality. Survival was increased in male and female rats offered amifampridine phosphate in diet compared to control group rats. Survival at the end of the dosing phase was 47%, 67%, 73%, and 72% for males, and 48%, 65%, 60%, and 73% for females for dose levels of 0, 8, 25, and 55 mg/kg/day, respectively.

Benign and malignant Schwannomas were only observed in male and female rats given amifampridine phosphate. In male rats, incidence of Schwannoma was comparable between rats given 25 and 55 mg/kg/day. In female rats, incidence was similar to the male rats at 8 and 25 mg/kg/day with an increased incidence at the highest dose (55 mg/kg/day).

Endometrial carcinomas were observed with an incidence of 0, 4, 13 and 9 for females offered 0, 8, 25 and 55 mg/kg/day amifampridine phosphate. A vast majority (22/26 tumors) of these tumors were observed after Study Week 100 and the remaining four were observed in rats between Study Weeks 86-99. The late onset of these tumors parallels the extended survival noted in test article-treated rats. The late appearance of these suggests the tumors arise from an epigenetic (non-genotoxic) mechanism, and as the endometrium is responsive to estrogenic activity, dose-related changes in pituitary/endocrine axis is the most likely epigenetic factor involved with this response.

The dose levels of 25 and 55 mg/kg/day amifampridine phosphate in males, and the dose levels of 8, 25, and 55 mg/kg/day in females were associated with a higher incidence of benign and malignant Schwannomas. Consequently, the no observed adverse effect level (NOAEL) was considered 8 mg/kg/day in males and <8 mg/kg/day in females.

6.4 Previous Clinical Studies

Amifampridine has been used for over 25 years in patients with multiple neurologic disorders including MG, CMS, LEMS, MS, ALS, congenital forms of nystagmus, and adult idiopathic nystagmus (AIN). There are a limited number of published controlled trials with amifampridine in these disorders. A review of the literature documents that amifampridine is a safe and effective treatment in multiple neurologic disorders and is recommended by the EFNS for first-line symptomatic treatment of patients with LEMS ([Skeie, 2006](#); [Skeie, 2010](#); [Lindquist, 2011](#)).

6.4.1 Amifampridine Phosphate in Healthy Subjects

A first in human Phase 1 study ([DAPSEL Study, 2006](#)) with amifampridine phosphate was conducted to investigate the bioavailability/bioequivalence and tolerability of amifampridine administered as a phosphate salt or free base. In the first part of the study, a pilot tolerance study was conducted in 5 healthy male volunteers who received a single 10-mg dose of amifampridine phosphate to determine tolerability. In the second part of the study, bioequivalence testing was conducted in 27 healthy male volunteers. Each patient was

randomized to receive either a single dose (2×10 mg tablets) of amifampridine as amifampridine phosphate or amifampridine base and received alternate treatment following a minimum of 72-hour washout period.

This study demonstrated bioequivalence for area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$), with the 90% confidence interval (CI) for the base/salt ratio of 93.1% to 113.3% falling within the predefined limits of 90% to 125% for bioequivalence. The mean elimination half-life ($t_{1/2}$) of amifampridine was 1.8 hours for the phosphate and 1.6 hours for the free base form. Amifampridine C_{max} was 64.8 ng/mL for the phosphate and 57.0 ng/mL for the free base form. Potentially improved absorption of the phosphate salt explained the slightly higher C_{max} observed for amifampridine phosphate compared with the free base. All adverse events (AEs) were mild or moderate, transitory and fully reversible. The nature and frequency of side-effects did not differ between formulations (phosphate salt or base). The most common AE (25 of 40 AEs) was paresthesia, which was mainly minor perioral paresthesia. Since paresthesia is well recognized as an AE occurring in patients treated with amifampridine, all were considered as possibly related to investigational product (IP) by the investigator. The only other AE occurring in >1 patient and judged possibly related to amifampridine was abdominal pain (4 events). Simple flu (5 events) and feeling of discomfort (2 events) were also reported for >1 patient in the study, however were considered not related to amifampridine treatment.

The only SAEs reported in the study were minor, isolated, and reversible increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which occurred in a single patient after administration of 20 mg amifampridine base. Aside from this 1 patient, no other laboratory abnormalities were observed. No electrocardiogram (ECG) abnormalities were observed. No deaths occurred in the [DAPSEL study](#).

A Phase 1 study (LMS-001) in healthy volunteers evaluated whether food consumption significantly affected the bioavailability of amifampridine phosphate tablets. This was an open-label, randomized, single-dose, 2-treatment, 2-period crossover design in 46 healthy volunteers. Each patient received 20 mg amifampridine phosphate on 2 occasions, once fasting and once after consumption of a standard high fat breakfast. The 2 single 20 mg doses of amifampridine phosphate were administered 6 days apart. Data indicate that taking amifampridine with food reduces exposures determined by C_{max} (maximum serum levels) by

approximately 40% and AUC by approximately 20%. In addition, the time to maximum serum concentrations (T_{\max}) was increased 2-fold from approximately 38 minutes (fasted) to 78 minutes (fed). The drug was well tolerated with no serious adverse events and only 1 severe event, an episode of gastroenteritis unrelated to amifampridine. The most common adverse events occurring in $\geq 10\%$ of patients were: oral paresthesia (20 patients; 43%), peripheral paresthesias (12; 26%), dizziness (5; 11%), headache (5; 11%), and oral hypoesthesia (5; 11%). Abdominal pain, nausea, peripheral paresthesias, dizziness, and headache were more commonly reported by patients following administration of amifampridine phosphate in the fasted state; therefore, administration with food is recommended based on the current study.

In both Study [LMS-001](#) and [DAPSEL](#), PK parameters were highly variable with 10-fold ranges observed in values of C_{\max} , AUC, and $t_{1/2}$ across patients. In humans, amifampridine is exclusively metabolized to a single major metabolite, 3-N-acetyl amifampridine, via N-acetyl transferases (NAT) (Catalyst internal *in vitro* and *in vivo* studies; data available upon request). There are 2 NAT enzymes, NAT1 and NAT2, both of which are principally hepatic and both of which are highly polymorphic. These allelic variations lead to slow and fast metabolism variations, which have been well characterized in the Caucasian and Asian populations, but somewhat less well in African populations ([Sabbagh, 2006](#)). Slow acetylators are estimated to comprise 50% to 59% of the Caucasian population, with the remainder being rapid acetylators (fast + intermediate). Fast acetylators are over represented in Asian population (92% of Japanese and 80% of Chinese) while they may be under represented in African populations (25%) ([Cascorbi, 1995](#)). Slow acetylators will accumulate drug to higher levels (i.e. higher C_{\max}) and clear drug more slowly (i.e. longer $t_{1/2}$), both of which may increase the risk of drug related toxicity ([Fukino, 2008](#); [Jetter, 2009](#)). It is hypothesized that the high variability in amifampridine phosphate PK may be due to NAT polymorphisms with slow and fast acetylator phenotypes. In a study (FIR-001) that evaluated the effect of acetylator status in 26 healthy subjects (half with fast and half with slow acetylator phenotypes), polymorphisms in the NAT system created 3- to 4-fold differences in plasma amifampridine levels. Potentially information relating NAT genotype and amifampridine phosphate PK could be used to inform dose selection for individual patients and to lower incidence of dose-related side effects.

6.4.2 Efficacy of Amifampridine in LEMS

A Phase 3, randomized, double-blind, placebo-controlled study ([LMS-002](#)) evaluated the efficacy and safety of amifampridine tablets 10 mg, as amifampridine phosphate (30-80 mg

total daily dose) versus placebo in patients with LEMS. The 38 patients treated with amifampridine phosphate had statistically significant improvement in both primary efficacy measures relative to patients treated with placebo. The change in QMG scores from baseline (Day 1, Part 2) to Day 14 (Part 3) reached statistical significance ($p=0.0452$), with the least square (LS) mean for QMG score increasing by 2.2 in placebo-treated patients, and increasing by 0.4 in amifampridine-treated patients. For the other primary endpoint, subject global impression (SGI), patients who were receiving amifampridine on Day 1 reported, on average, that they were “pleased” (SGI score of 5.9 ± 1.2) with the test medication while they were receiving it. After being switched to placebo tablets, their opinions dropped, on average, 2.7 ± 2.3 points. The LS mean was -2.6 for the placebo group and -0.8 for the amifampridine group, a difference of 1.8 ± 0.6 ($p=0.0028$), corresponding to a patient assessment, of “mixed” for the placebo tablets. This substantial change in patients’ assessments, to a worsening of their condition while receiving placebo, was considered clinically significant.

In addition to Study [LMS-002](#), 5 randomized, double-blind, placebo-controlled studies and 1 double-blind study with an active comparator (reported in abstract form only) in 71 patients with LEMS are reported in the clinical literature. In all 6 studies, amifampridine (in base form) was shown to be more effective for the symptomatic treatment of LEMS compared with placebo or active comparator across a number of independent measures of neurological function. Supportive data from multiple published uncontrolled investigations and case reports demonstrate the long-term benefits of treatment with amifampridine in patients with LEMS, and show that removal of patients from drug has led to recurrence of underlying symptoms. Refer to the [Firdapse Investigator Brochure](#) (February, 2015) for further details on these studies.

6.4.3 Safety of Amifampridine and Amifampridine Phosphate

Safety data collected from 1,455 patients or healthy volunteers in controlled study [LMS-002](#) (LEMS), controlled and uncontrolled published studies of LEMS or other neurologic conditions, a 3-year safety surveillance study (ATU), and PK studies demonstrate amifampridine is well tolerated up to and including 80 mg/day ([Firdapse Investigator Brochure, February 2015](#)). The most common adverse events observed from the clinical safety data were perioral and peripheral paresthesias and gastrointestinal disorders (abdominal pain, nausea, diarrhea, epigastralgia). These events were typically mild or moderate in severity, and transient, seldom requiring dose reduction or withdrawal from treatment. In the

pharmacogenomic study in healthy subjects (classified as either slow acetylators or fast acetylators), slow acetylators experienced >80% more drug-related AEs compared with fast acetylators ([FIR-001](#)).

Clinically significant or serious adverse events were infrequent in all studies for all indications. A total of 12 deaths were reported in the 1,455 patients or healthy subjects. Six of 12 deaths were associated with accompanying malignancy (1 of 6 with pulmonary embolus as terminal event), 1 due to tracheobronchitis, and 2 due to myocardial infarction (MI). Attribution to amifampridine for 2 of 3 deaths from the ATU study was specified as unrelated; causality for the third death was not reported. No attribution was specified in the academic series, but the author singled out the fatal MI as the only serious incident during amifampridine therapy, implying that the 2 deaths due to malignancy, the 1 due to malignancy and pulmonary embolus and the 1 due to tracheobronchitis were not related in his opinion. The author further states that no pathological findings related to amifampridine were found in the patient who died of tracheobronchitis. For 1 of the fatal MIs, the author speculates that a “sudden increase of physical activity” with amifampridine may have been a contributant ([Lundh, 1984](#); [Lundh, 1993](#)); no causality was reported for the other fatal MI ([Bertorini, 2011](#)). Three deaths occurred in children with CMS, including 2 with fast-channel CMS ([Beeson, 2005](#)). Although no causal relationship was established with amifampridine, the authors advise its use cautiously in children and in fast-channel patients. The other CMS death was not thought to be related to amifampridine ([Palace, 1991](#)). Overall 7 of 12 deaths were not considered related to amifampridine; neither cause nor causality is known for 4 deaths; and amifampridine may have contributed indirectly to 1 of the MI-related deaths.

The most frequent clinically significant or serious event was seizure. A total of 11 (0.76%) patients out of 1,455 patients or healthy subjects experienced seizures or convulsions after treatment with amifampridine. Electroencephalogram findings, reported for 4 of the 11 patients, did not show epileptiform activity. Four of 11 seizures occurred in patients with LEMS (4/209; 1.91%), 4 occurred in patients with MS (4/774; 0.5%), 1 occurred in a patient with CMS (1/88; 1.14%) ([Harper, 2000](#)) and 2 seizures were reported in a literature-based study where both MG and LEMS patients were enrolled, but the paper did not state the indication ([Sanders, 1993](#); [Sanders, 2000](#); [Flet, 2010](#); [McEvoy, 1989](#); [Boerma, 1995](#); [Bever, 1996](#)).

Amifampridine was implicated in 5 of these cases of seizure. Three patients experienced seizures on a daily dose of ≥ 90 mg/day (n=3; LEMS or MG). Contributing factors for seizures were a daily dose of ≥ 90 mg/day, concurrent treatment with theophylline, brain metastases,

and a case of drug overdose (360 mg/day for 7 days). In cases where follow-up was reported, most seizures did not recur with amifampridine dose reduction or treatment withdrawal. In the one accidental overdose case, seizures were controlled with intravenous clonazepam and the patient made a full recovery ([Boerma, 1995](#)). Note that a seizure rate of 4% can be expected in the natural course of patients with MS ([Engelsen, 1997](#); [Moreau, 1998](#); [Kinnunen, 1987](#)). Among the 774 MS patients treated with amifampridine included in the safety assessment of this report, 4 (0.5%) experienced seizures.

Other clinically significant or SAEs reported in more than 1 adult patient were palpitations (8/1,454; 0.56%), abnormal liver enzymes (6/1,454; 0.41%), QTc prolongation (2/1,454; 0.14%), and premature ventricular contraction/increased ventricular extrasystoles (2/1,454; 0.14%). Each of the following serious or clinically significant events was reported in a single patient: chorea, paresthesias, paroxysmal supraventricular tachycardia, cardiac arrest, drug-induced hepatitis, gastroesophageal reflux, increased lipase and amylase, aspiration pneumonia with confusion, and urinary tract infection with confusion.

6.4.4 Overall Risks and Benefits

Data on amifampridine treatment in patients or healthy volunteers support the favorable safety profile of amifampridine (both base and phosphate formulations) at doses up to 80 mg per day. Current data demonstrate that amifampridine phosphate salt has an acceptable tolerability profile with a positive risk-benefit in patients treated with amifampridine. Refer to the [Firdapse Investigator Brochure \(February, 2015\)](#) for further discussion on benefit/risk of amifampridine.

6.4.5 Study Rationale

As discussed previously, a considerable amount of clinical experience is available with amifampridine (3,4-diaminopyridine; 3,4-DAP) in patients with LEMS and other neurologic disorders and, in December 2009, amifampridine phosphate received marketing approval by the European Commission as Firdapse for the symptomatic treatment of patients with LEMS. [LMS-002](#) also provided Class 1 evidence that amifampridine phosphate provides statistically and clinically significant improvement in LEMS patients. LMS-003 represents a second efficacy study.

7 STUDY OBJECTIVES

7.1 Primary Objectives

The primary objectives of the study are:

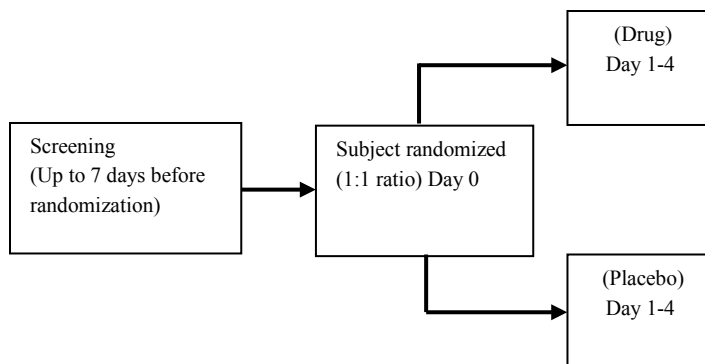
- To assess the clinical efficacy of amifampridine phosphate compared to placebo in subjects with LEMS, based upon improvement in subject global impression (SGI) and quantitative myasthenia gravis (QMG) score; and
- To confirm the safety and tolerability of amifampridine phosphate by adverse event reports.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This randomized (1:1), double-blind, placebo-controlled, parallel-group study is designed to evaluate the efficacy and safety of amifampridine phosphate in patients diagnosed with LEMS. Patients will have been receiving unblinded drug treatment in the expanded access program (EAP-001), after which blinded treatment effect will be assessed for continuation or cessation of drug. The study is planned to include approximately 28 male and female patients. The planned duration of participation for each patient is 5 days, excluding the screening period, which can last up to 7 days.

Those patients successfully satisfying all screening criteria will be randomized to a treatment group. Amifampridine phosphate (at the patient's optimal dose) or placebo will be dispensed by the site pharmacist, according to the randomization schedule, to begin with the next dose after all Day 0 assessments are completed and continued for 4 days. After completion of the study, patients will be eligible for expanded access treatment program with open-label amifampridine phosphate. Since patients will have been out of the expanded access program for less than 30 days, as LMS-003 participants, rescreening to return to expanded access program will not be required, per the protocol, and patients may immediately resume their participation in the expanded access program (EAP-001).



Screening

Patients receiving amifampridine phosphate treatment for LEMS, and meeting the inclusion and exclusion criteria are eligible to participate in this study. They can be randomized if on stable dose and frequency of amifampridine phosphate for at least 1 week before being randomized to a treatment. Screening and randomization (Day 0) may be combined into a single visit.

Treatment (Days 1-4) (+1 day)

Patients will be randomized (1:1 ratio) on the last day of the screening period (Day 0) to either amifampridine phosphate or placebo. Beginning with the next dose after all Day 0 assessments are completed, the patient will take, under double-blind conditions, either amifampridine phosphate tablets or placebo tablets through Day 4, with a clinic visit on the last day (Day 4) for assessments ([Table 3](#)). Any unused portion of dispensed drug will be returned to the pharmacy.

During the study, safety and efficacy assessments will be made as detailed in the Schedule of Assessments in [Table 3](#).

Table 3. Schedule of Assessments

Study Assessment or Event	Screening	Randomization	Days 1-4
	Days -7 to -1	Day 0	Day 4 (+1 d)
Informed consent	X		
Inclusion/exclusion criteria	X		
Randomization		X	
Medical history	X		
Physical exam	X		
Vital signs	X		X
‘Liquid biopsy’ blood sample ¹	X		
Urine sample for amifampridine level ²			X
Pregnancy test – urine ³	X		
Blinded IP dispense		X	
IP accountability			X
CGI-I			X
SGI		X	X
QMG		X	X
3TUG		X	X
Patient most bothersome symptom question		X	X
Concomitant medications	X	X	X
Adverse Events	X	X	X

¹Optional test, at patient’s discretion

²Urine specimen for amifampridine level will be collected on Days 3 and 4

³Women of child-bearing potential

8.2 Selection of Study Population

Criteria for participation in the study are provided in Sections [8.2.1](#) and [8.2.2](#).

8.2.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following inclusion criteria:

1. Male or female ≥ 18 years of age with LEMS and currently receiving a stable dose of amifampridine phosphate for at least 7 days.
2. Diagnosis of LEMS by antibody testing or EMG.
3. Completion of anti-cancer treatment at least 3 months (90 days) prior to Screening.
4. If receiving peripherally acting cholinesterase inhibitors (e.g. pyridostigmine), a stable dose of cholinesterase inhibitors is required for at least 7 days prior to randomization and throughout the study.
5. If receiving permitted oral immunosuppressants (prednisone or other corticosteroid), a stable dose is required for at least 30 days prior to randomization and throughout the study.
6. Female patients of childbearing potential must practice effective, reliable contraceptive regimen during the study.
7. Able to perform all study procedures and assessments.
8. Willing and able to travel to study site and attend all clinic study visits.
9. Willing and able to provide written informed consent.

8.2.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria are not eligible to participate in the study:

1. Clinically significant long QTc interval on ECG in previous 12 months.
2. Seizure disorder.
3. Active brain metastases.
4. Unable to ambulate
5. Pregnant or lactating females.
6. Any other condition which, in the opinion of the investigator, might interfere with the patient's participation in the study or confound the assessment of the patient.
7. Patients who cannot discontinue immunomodulatory treatment (e.g. mycophenolate, azathioprine, cyclosporine) within 3 weeks before screening.

8.2.3 Removal of Patients from Treatment or Assessment

Patients may withdraw their consent to participate in the study or refuse to receive treatment with IP at any time without prejudice. The investigator must withdraw from the study or from treatment with IP any patient who requests to be withdrawn. A patient's participation in the study or treatment with IP may be discontinued at any time at the discretion of the investigator and in accordance with his or her clinical judgment. In the event that the patient's LEMS symptoms worsen to a clinically significant level, in the opinion of the Investigator, the patient may be placed on open-label amifampridine phosphate, and Early Discontinuation assessments should be performed as described for Day 4 ([Table 3](#)).

Catalyst must be notified of all patient withdrawals from the study or from treatment with IP as soon as possible. Catalyst also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance.

Reasons for which the Investigator or Catalyst may withdraw a patient from the study treatment include, but are not limited to, the following:

- Patient experiences a serious or intolerable AE;
- Patient requires medication prohibited by the protocol; and
- Patient becomes pregnant.

Reasons for which the Investigator or Catalyst may withdraw a patient from the study include, but are not limited to, the following:

- Patient does not adhere to study requirements specified in the protocol;
- Patient was erroneously admitted into the study or does not meet inclusion criteria; and
- Patient is lost to follow-up.

If a patient fails to return for scheduled visits, a documented effort must be made to determine the reason. If the patient cannot be reached by telephone, a certified letter should be sent to the patient requesting contact with the Investigator. This information should be recorded in the study records.

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with Catalyst, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information, per country-specific regulations, from each patient. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the patient and the patient will be removed from the study.

8.2.4 Patient Identification and Randomization

Each patient will be assigned a unique patient identification number. Upon signing of the ICF, subjects will be assigned an ID composed of a 2 digit site number and a 3 or 4 digit subject number. Screen failures that are allowed to repeat screening ([Section 8.2.5](#)) will be assigned a new ID and the previous ID will be kept as part of the record. Randomized subjects that drop out of the study may be replaced.

Randomization will be across sites to maintain the 1:1 ratio of drug: placebo assignment. The assignments to treatment (amifampridine phosphate or placebo) will be based on a computer-generated randomization code. Study site Pharmacy will obtain the treatment group for the subject to be enrolled at the time of randomization (Day 0).

8.2.5 Re-screening

Re-screening of screen failures will be allowed, if re-screening is approved by the Medical Monitor. Justification of the reason for re-screening must be clearly stated in the patient's source documentation. No new consent would be required if re-screened within 30 days.

8.3 Treatments

8.3.1 Treatments Administered

Catalyst or its designee will provide the study site with a supply of IP sufficient for the completion of the study.

Investigational product: Amifampridine phosphate tablets 10 mg will be provided in round,

white-scored tablets, and containing amifampridine phosphate formulated to be the equivalent of 10 mg amifampridine base per tablet. The product will be provided to the site pharmacy department, who will dispense the necessary amount for each part of the study.

The product will be blinded, neither the investigator nor the patient will know what product they are assigned.

Placebo: A placebo equivalent will be provided as tablets indistinguishable from the amifampridine phosphate tablets. The placebo will be administered consistent with the dose regimen of amifampridine phosphate. The product will be blinded, neither the Investigator nor the patient will know what product they are assigned.

8.3.2 Identity of Investigational Product

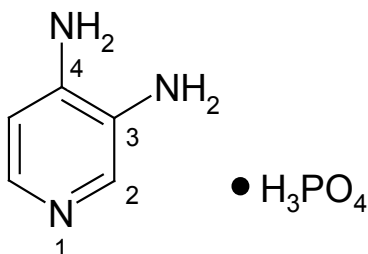
The chemical name of amifampridine phosphate is:

3,4-pyridinediamine, phosphate (1:1) diamino-3,4-pyridine, phosphate salt

3,4-diaminopyridine phosphate

The chemical structure is provided in [Figure 1](#).

Figure 1. Chemical Structure of Amifampridine Phosphate



8.3.2.1 Product Characteristics and Labeling

Drug product is formulated as a phosphate salt of amifampridine. Tablets were developed to provide the equivalent of 10 mg of amifampridine base for oral administration. Each tablet contains amifampridine phosphate, microcrystalline cellulose, colloidal anhydrous silica, and calcium stearate. The containers of tablets are labeled “Amifampridine phosphate Tablets, 10 mg.”

The tablets are to be dispensed by the site pharmacy department into suitably sized pharmacy containers for patient use. Placebo will be provided as tablets indistinguishable from amifampridine phosphate. The amifampridine phosphate tablets and placebo tablets will be

clearly labeled and the pharmacist is responsible for dispensing the amifampridine phosphate tablets or placebo tablets, in a blinded fashion, for each patient, according to the randomization schedule provided.

Each container will be labeled to include the study number, site number, patient ID number, date dispensed, storage instructions, the statement ‘Caution – New Drug – Limited by Federal law to investigational use,’ trial number, manufacturer name and address, and area for instructions for use.

8.3.2.2 Storage

At the study site, all IP must be stored at room temperature (20-25 degrees Celsius) and in a secure area accessible only to the designated pharmacist and clinical site personnel. All IP must be stored and inventoried, and the inventories must be carefully and accurately documented according to applicable national and local regulations, ICH GCP, and study procedures.

8.3.3 Directions for Administration

The dose of amifampridine phosphate will be individually determined by the Investigator, within the bounds of a total daily dose of 30 mg to 80 mg, divided into doses taken 3 to 4 times per day as prescribed by the Investigator, based on optimal neuromuscular benefit.

All doses of study medication will be taken orally by mouth.

Generally, doses of study treatment will be taken outside the clinic, **except** during the in-clinic study visit. If the patient takes the dose three or four times a day, the patient should be given specific instructions on dosing relative to the time of their visit to assure a dose will be given during the in-clinic visit, corresponding to the second, third, or fourth dose. **A dose must be administered in the clinic in order to perform efficacy assessments at the correct time in relation to dosing.** Safety assessments are to be performed **before the dose** administered to the patient during the scheduled in-clinic visit. All efficacy assessments will be performed at times relative to the dose administered in the clinic. **In this case, the dose will be 40 minutes before the first efficacy assessment.**

Assessment	Start Time <u>After Dose*</u> (+ 10 minutes unless otherwise specified)
SGI	40 minutes
Patient most bothersome symptom	Following SGI
QMG	Following patient symptom evaluation
CGI-I°	Following QMG
3TUG	Following CGI-I

*Administration of medication represents Time 0 (minutes)

°Except on Day 0

If the patient is taking pyridostigmine, the dosing schedule must be fixed in relation to when they take the IP, such that on the days of clinic assessments the timing between pyridostigmine dose and IP do not vary.

Assessments for each clinic visit must be performed relative to the same dose as occurred on Day 0.

8.3.4 Method of Assigning Patients to Treatment Groups

Patients will be randomized Day 0 to either treatment group in a 1:1 ratio. IP will be administered under double-blind conditions such that neither the Investigator nor patient knows if they are taking placebo or amifampridine phosphate.

The randomization code will be provided by Catalyst or designee to the site Pharmacist. Details will be included in the Pharmacy Manual.

8.3.5 Selection of Doses Used in the Study

The amifampridine phosphate dose is 30 mg to 80 mg total daily dose, given in 3 to 4 divided doses, with no single dose >20 mg. Safety of a single maximum dose of 20 mg is based on completed animal and *in vitro* pharmacology, PK, and toxicology studies.

8.3.6 Blinding

This is a double-blind study where both the patients and Investigator will be blinded to treatment assignment.

8.3.7 Treatment Compliance

Patients will be instructed to return all IP containers and remaining study medication at the study clinic visit. Patient compliance with the dosing regimen will be assessed by reconciliation of the used and unused IP. The quantity dispensed, returned, used, lost, etc., must be recorded on the medication dispensing log provided for the study. Urine specimens will be collected to further assess treatment compliance.

8.3.8 Investigational Product Accountability

The study site pharmacy is responsible for maintaining accurate records (including dates and quantities) of IP(s) received, patients to whom IP is dispensed (patient-by-patient dose specific accounting), IP returned, and IP lost or destroyed. The Investigator, study site pharmacy or designee must retain all unused or expired study supplies until the study monitor (CRA) has confirmed the accountability data.

8.3.9 Return and Disposition of Clinical Supplies

Unused IP must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or designee must provide an explanation for any destroyed or missing IP or study materials.

The monitor must account for all IP in a formal reconciliation process prior to IP destruction. Unused IP will be returned to Catalyst. The return of IP or IP materials must be accounted for on a Study Drug Return Form provided by Catalyst.

All IP and related materials should be stored, inventoried, reconciled, and returned according to applicable study procedures.

8.4 Prior and Concomitant Medications

All prescription and over-the-counter medications and herbal and nutritional supplements taken by a patient for 14 days before the Screening visit will be recorded on the designated case report form (CRF).

The Investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the Medical Monitor must be notified of the use of any contraindicated medications immediately thereafter. Any concomitant medications added or discontinued during the study should be recorded on the CRF.

Medications prohibited during the study are listed in [Table 4](#).

Table 4. Medications Prohibited Before and During Study

Immunomodulatory treatment (e.g. azothiaprime, mycophenolate, cyclosporine) within 3 weeks before Screening
IVIG within 2 weeks before Screening
Plasmapheresis (PE or TPE) within 3 weeks before Screening
Rituximab within 6 months before Screening
Any investigational product (other than amifampridine phosphate) or an investigational medical device within 30 days before Screening
Products with atropinic effects

8.5 Dietary or Other Protocol Restrictions

8.5.1 Dietary Restrictions

There are no dietary restrictions for patients during any part of this study.

8.5.2 Contraception

Sexually active males and females of childbearing potential must use effective forms of contraception, such as condom for males or occlusive cap (diaphragm or cervical/vault caps) for females, during the study.

8.6 Safety Variables

Safety in this study will be determined from evaluation of AEs/SAEs, vital signs assessments, and physical examinations. Pregnancy testing is also required for females of childbearing potential. The timing of the required evaluations is described in the Schedule of Events in [Table 3](#).

8.6.1 Adverse Events

The determination, evaluation and reporting of AEs will be performed as outlined in [Adverse Events](#).

8.6.2 Vital Signs

Specific visits for obtaining vital signs are provided in [Table 3](#) and in [Section 11](#). Vital signs will be measured while in a sitting position, after resting for 5 minutes, and include SBP and DBP measured in millimeters of mercury (mmHg), heart rate in beats per minute. Weight (kg) and temperature in degrees Celsius (°C) will also be measured. Clinically significant changes from baseline will be recorded as AEs.

8.6.3 Clinical Laboratory Assessments

Since LEMS can be associated with neoplastic disease, all patients who enter the trial will have the option to participate in cancer screening using the ‘liquid biopsy’ technique, every 6 months for 2 years.

The procedure involves collecting tubes of blood which is then incubated with a variety of antibodies directed towards circulating tumor cells. Additional analysis of identified cells may then be performed. Follow-up screening will be performed by expanded access clinical sites.

8.6.4 Pregnancy Testing

Female patients of childbearing potential will have a urine pregnancy test at Screening. If the test is equivocal or there is another concern about pregnancy, a serum pregnancy test may be performed. Female patients with a positive pregnancy test at Screening do not meet eligibility criteria for enrollment.

Refer to Section 9.4 for details on the reporting procedures to follow in the event of pregnancy.

8.6.5 Physical Examination

A complete physical examination will be performed at the time points specified in the Schedule of Events in [Table 3](#) and in [Section 11](#). Complete physical examination will include assessments of general appearance as well as the following:

- Head

- Eyes
- Ears
- Nose
- Throat
- Cardiovascular
- Dermatologic
- Lymphatic
- Respiratory
- Gastrointestinal

Other body systems may be examined. Clinically significant changes from baseline will be recorded as AEs.

8.7 Efficacy Variables

The timing of required evaluation is described in the Schedule of Events in [Table 3](#) according to the sequence listed below.

Assessment	Start Time <u>After Dose*</u> (+ 10 minutes unless otherwise specified)
SGI	40 minutes
Patient most bothersome symptom	Following SGI
QMG	Following patient symptom evaluation
CGI-I°	Following QMG
3TUG	Following CGI-I

*Administration of medication represents Time 0 (minutes)

°Except on Day 0

Primary Efficacy Variables

8.7.1 Subject Global Impression

The SGI ([Farrar, 2001](#)) is a 7-point scale on which the patient rates their global impression of the effects of a study treatment (1 = terrible to 7 = delighted). The SGI will be assessed by the patient or the patient's parent/guardian/caregiver if the patient is unable to complete the SGI.

The SGI has demonstrated concordance with the physician's assessment of improvement ([Dodick, 2007](#)). Instructions for the SGI are provided in [Appendix 2](#) and the LMS-003 Study Reference Manual.

8.7.2 Quantitative Myasthenia Gravis

The QMG is a physician-rated test including 13 assessments such as facial strength, swallowing, grip strength, and duration of time that limbs can be maintained in outstretched positions. The QMG was first developed by Besinger ([Besinger, 1983](#)), expanded by Tindall ([Tindall, 1993](#); [Tindall, 1987](#)); and subsequently further modified by Barohn ([Appendix 1](#)) ([Barohn, 1998](#)). His modified QMG has been assessed for inter-rater reliability and was used as the outcome measure in a prospective study of IVIG for MG ([Wolfe, 2002](#)) and two studies of amifampridine for LEMS ([Sanders, 2000](#); [Oh, 2009](#)). Instructions for conducting the QMG are provided in [Appendix 1](#) and the LMS-003 Study Reference Manual.

Secondary Efficacy Variable

8.7.3 Clinical Global Impression of Improvement

The CGI-I captures the Investigator's global impression of the patient's improvement or worsening from baseline status. The 7-point scale is scored by the Investigator based on changes in symptoms, behavior, and functional abilities. Instructions for the CGI-I are contained in [Appendix 3](#) and the LMS-003 Study Reference Manual.

Exploratory Efficacy Variables

8.7.4 Triple Timed Up and Go (3TUG) – greater than 20% increase in average time, off medication

The Timed Up and Go (TUG) is a functional mobility test that requires a subject to stand up from a straight-backed armchair, walk 3 meters, turn around, walk back, and sit down in the chair. A modification of this is where the individual performs the test three times without pause, and the measurement is the average time required to complete each of the 3 repetitions. Based upon literature reports that a significant change in gait for a similar walk-test is an increase in time of more than 20%, this has been incorporated into the endpoint.

Instructions for the 3TUG are contained in [Appendix 4](#) and the LMS-003 Study Reference Manual.

8.7.5 Patient Evaluation of Most Bothersome Symptom

Patients identify their most bothersome LEMS-associated symptom as a measure of patient satisfaction with the treatment. The evaluation consists of 2 questions, the first is to identify before treatment or while off medication, what the patient perceived as their most bothersome symptom and the level to which it bothered them, on a 4 point scale. Following blinded treatment with study medication, the patient is asked to evaluate how much the previously identified symptom bothered them during the prior 24 hours, on the same 4 point scale.

The Symptom Scale is contained in Appendix 5 and the LMS-003 Study Reference Manual.

9 REPORTING ADVERSE EVENTS

9.1 Adverse Events

For this protocol, a reportable AE is any untoward medical occurrence (e.g. sign, symptom, illness, disease or injury) in a patient administered the IP or other protocol-imposed intervention, regardless of attribution. This includes:

- AEs not previously observed in the patient that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions.

An adverse drug reaction is any AE for which there is a reasonable possibility that the IP caused the AE. “Reasonable possibility” means there is evidence to suggest a causal relationship between the IP and the AE.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

The study period during which all serious and non-serious AEs will be reported begins after informed consent is obtained and through the last visit on Study Day 4, or at the time of early

discontinuation. The criteria for determining, and the reporting of SAEs is provided in [Section 9.2](#).

The Investigator should follow all unresolved AEs until the events are resolved or stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE. Resolution of AEs (with dates) should be documented on the appropriate CRF page(s) and in the patient's medical record.

The Investigator responsible for the care of the patient or qualified designee will assess AEs for severity, relationship to IP, and seriousness (refer to [Section 9.2](#) for SAE definition). Severity (as in mild, moderate or severe headache) is not equivalent to seriousness, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

The Investigator will determine the severity of each AE using the following Common Terminology Criteria for Adverse Events (CTCAE v4) grades defined in [Table 5](#) (the event will be recorded on the source documents and AE CRF). Events that are CTCAE grades 4 and 5 are serious events and require completion of both an SAE form and AE CRF. Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE as stated below.

Table 5. Categories of Severity for CTCAE Criteria

Severity	Description	
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.	
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.	
Grade 4	Life-threatening consequences; urgent intervention indicated.	Note: Grade 4 and 5 adverse events should always be reported as serious adverse events
Grade 5	Death related to AE.	

Activities of Daily Living (ADL)

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The Investigator will suggest the relationship of an AE to the IP and will record it on the source documents and AE CRF, using the relationship categories defined in [Table 6](#).

The Investigator should review the AE Log for the patient, from the EAP-001 expanded access program. Any ongoing/open/unresolved AEs will be transcribed to the LMS-003 study AE Log. At the end of patient's participation in the LMS-003 study, the AE Log should be provided to the expanded access program site, so that the expanded access site can update their AE Log with any changes.

Table 6. Description of Relationship to Adverse Event Categories

Relationship Category	Description
Not Related	Exposure to the IP has not occurred OR The administration of the IP and the occurrence of the AE are not reasonably related in time OR The AE is considered likely to be related to an etiology other than the use of the IP; that is, there are no facts [evidence] or arguments to suggest a causal relationship to the IP.
Possibly Related	The administration of the IP and the occurrence of the AE are reasonably related in time AND The AE could be explained equally well by factors or causes other than exposure to the IP.
Probably Related	The administration of IP and the occurrence of the AE are reasonably related in time AND The AE is more likely explained by exposure to the IP than by other factors or causes.

In order to classify AEs and diseases, preferred terms will be assigned by the sponsor to the original terms entered in the eCRF, using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

9.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Is fatal
- Is life threatening
 - *Note: Life-threatening refers to an event that places the patient at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death*
- Requires or prolongs in-patient hospitalization
- Results in persistent or significant disability or incapacity

- Is a congenital anomaly or birth defect, that is, an AE that occurs in the child or fetus of a patient exposed to IP prior to conception or during pregnancy
- Is an important medical event or reaction.

For this study, a generalized tonic-clonic convulsion/seizure is to be considered an SAE.

Any SAE, whether or not considered related to study drug, must be reported within 24 hours of knowledge of the event by forwarding (fax, email) the study-specific SAE Report Form to Catalyst. The Investigator should not wait to collect information that fully documents the SAE before notifying Catalyst. As additional information becomes available, including but not limited to the outcome of the SAE and any medication or other therapeutic measures used to treat the event, it must be reported within 24 hours in a follow-up report to Catalyst.

The Investigator should follow all unresolved SAEs until the events are resolved or stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE. Resolution of AEs (with dates) should be documented in the eCRF and in the patient's medical record.

For some SAEs, Catalyst may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g. hospital discharge summary, consultant report, autopsy report).

At the last scheduled visit, the Investigator should instruct each patient to report any subsequent SAEs that the patient's personal physician(s) believes might be related to prior study treatment.

The Investigator should notify Catalyst of any death or SAE occurring at any time after a patient has discontinued, or terminated study participation, if felt to be related to prior study treatment. Catalyst should also be notified if the Investigator should become aware of the development of cancer, or of a congenital anomaly, in a subsequently conceived offspring of a patient that participated in this study.

Reporting of SAEs to the IRB will be done in compliance with the standard operating procedures and policies of the IRB and with applicable regulatory requirements. Adequate documentation must be provided showing that the IRB was properly and promptly notified as required.

9.3 Safety Blood Collection

Patients who experience a serious or severe AE should have, at the discretion of the Investigator, a blood sample drawn for safety labs as soon as possible after the AE.

Additional blood sampling may be performed at any time during the study if warranted to monitor patient safety.

9.4 Pregnancy

Pregnancy in a patient or partner should be reported within 24 hours of the site becoming aware of the pregnancy by fax or email of the Pregnancy Report Form in the study reference materials to Catalyst. In addition, pregnancy in a patient is also reported on the End of Study CRF. The Investigator must make every effort to follow the patient through resolution of the pregnancy (delivery or termination) and to report the resolution on the follow-up form (Pregnancy Report Form: Additional Information) in the study reference materials. In the event of pregnancy in the partner of a study patient, the Investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information.

9.5 Urgent Safety Measures

The regulations governing clinical trials state that the sponsor and Investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC (and consistent with the US FDA regulations at 21 CFR 56.108(a)), "...in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the Investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/EC/REB is notified at the same time." The reporting period for urgent safety measures is the period from the time of signing of the ICF through the completion of the last study visit. Investigators are required to report any urgent safety measures with 24 hours.

Examples of situations that may require urgent safety measures include discovery of the following:

- An immediate need to revise IP administration (i.e. modified dose amount or frequency not defined in protocol).
- Lack of study scientific value, or detrimental study conduct or management.
- Discovery that the quality or safety of IP does not meet established safety requirements.

9.6 Medical Monitor Contact Information

Contact information and additional requirements will be provided in the LMS-003 Study Reference Manual.

The Investigator is encouraged to discuss with the Medical Monitor any AEs for which the issue of seriousness is unclear or questioned. Contact information for the study Medical Monitor is listed below.

Gary Ingenito, MD, PhD
Chief Medical Officer
Catalyst Pharmaceuticals, Inc.
Tel: +1 305-420-3200, ext. 123
Email: gingenito@catalystpharma.com

10 APPROPRIATENESS OF MEASUREMENTS

The measures of safety used in this study are routine clinical procedures. The efficacy measures use a variety of approaches to evaluate changes in neuromuscular function and muscle strength. These standardized tests have been previously used for determination of response to therapeutic intervention in patients with MG and in other indications and, thus, are relevant for use in this study in patients with LEMS.

11 STUDY PROCEDURES

11.1 Screening Visit

An ICF must be signed and dated by the patient, the Investigator or designee, and witness (if required) before any study-related procedures are performed.

After patient has signed an ICF, they will be screened for enrollment into the study. The study activities listed below will be performed during the 7 days that constitute the Screening Visit.

- Informed Consent

- Assessment of Inclusion/Exclusion criteria
- Demographics (sex, race, ethnic origin, age)
- Medical history, including allergy history and number of hospitalizations or ER visits in last 6 months,
- History of orthopedic procedures that may affect walking or getting up out of a chair
- Method of LEMS diagnosis
- Complete physical examination including weight and height
- Vital signs (seated position), including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and body temperature
- Liquid biopsy specimen (if patient opts for cancer screening)
- Urine pregnancy test in females of childbearing potential only
- Assessment of AEs/SAEs
- Assessment of concomitant medications

11.2 Randomization Visit (Study Day 0)

The study activities listed below will be performed on Study Day 0, while the patient has been on open-label amifampridine phosphate and in relationship to the usual dosing schedule.

Assessment	Start Time <u>After Dose*</u> (+ 10 minutes unless otherwise specified)
SIG	40 minutes
Patient most bothersome symptom, Question 1	Following SIG
QMG	Following patient symptom evaluation
3TUG	Following QMG

*Administration of medication represents Time 0 (minutes)

- Assessment of AEs/SAEs
- Assessment of concomitant medications

Patients who are deemed eligible will be dispensed double-blind study medication (amifampridine phosphate or placebo tablets) on Study Day 0, according to the treatment group to which they are randomized. The patient's open-label amifampridine must be collected. **Patients must stop their open-label amifampridine and will start to take the blinded study**

medication beginning with the next scheduled dose after all assessments on open-label medication have been completed.

Patients must be instructed that they are not to take any doses of their prior, open-label amifampridine during the study and not to change pyridostigmine dose or schedule.

11.3 End of Treatment (Study Day 4)

Patients will take their blinded study medication on Days 1-3. On Day 4, a dose of blinded study medication must be administered by the site study personnel. This is the same medication that the patient has been taking on Days 1-3. The assessments listed below will be performed **following either the second, third, or fourth dose of medication to be taken on Day 4, and this should be the same dose that assessments on Day 0 were subsequently performed**. For example, if the patient took their second dose of amifampridine in the clinic on Day 0 and had assessments started 40 minutes later, then on Day 4, that patient should be assessed after taking their second dose of medication in the clinic, starting 40 minutes after the dose.

Safety assessments (vital signs and AEs/SAEs) should be performed before study personnel give the dose of blinded medication. Concomitant medications should be reviewed for any changes. A urine sample, to determine amifampridine level, should be collected on Day 3 (after patient has taken a dose of blinded medication), and on Day 4, before study personnel give the dose of blinded medication.

Assessment	Start Time <u>After Dose*</u> (+ 10 minutes unless otherwise specified)
SGI	40 minutes
Patient most bothersome symptom, Question 2	Following SGI
QMG	Following patient symptom evaluation
CGI-I (compared to Day 0)	Following QMG
3TUG	Following CGI-I

*Administration of medication represents Time 0 (minutes)

The container of blinded study medication dispensed on Study Day 0 must be returned to study personnel and the IP Accountability form completed to determine if the blinded study medication doses were taken.

This represents the end of the study.

11.4 Early Discontinuation Visit

Any patient that discontinues from the study, regardless of the reason, will be requested to complete all Early Discontinuation visit assessments/procedures as listed below after the last dose of study medication. Every reasonable effort should be made to contact any patient who is lost to follow-up.

In cases of Early Discontinuation, medication will have been stopped some time prior to seeing the patient for the below assessments. The date and time of the last dose of medication should be recorded in relation to when the assessments are performed.

- Assessment of AEs/SAEs
- Vital signs
- Concomitant medications
- IP accountability
- SGI
- CGI-I (compared to Day 0)
- Patient most bothersome symptom, Question 2
- QMG
- 3TUG

12 DATA QUALITY ASSURANCE

Catalyst personnel or designee(s) will visit the study site before initiation of the study to preview with the site personnel information about the IP, protocol and other regulatory document requirements, any applicable randomization procedures, source document requirements, CRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

At visits during and after the study, a CRA will monitor the site for compliance with regulatory documentation. Data quality control and analysis will be performed by Catalyst, or designee, based on a predefined plan.

13 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

13.1 Determination of Sample Size

For Change From Baseline in QMG Scores, a between-treatment difference of -3.5 and a standard deviation at most 3, a sample size of at least 24 patients will provide power of at least 80% for a 0.05 level test. Similarly, for Change From Baseline in SGI Scores, a between-treatment difference of -2.1 and a standard deviation at most 2, a sample size of at least 26 patients will provide power of 80% for a 0.05 level test. Thus a total sample size of 26 patients, equally randomized to two treatment sequences, will provide power of at least 80% for each of the two co-primary endpoints.

13.2 Patient Populations

Analyses will be presented for

- **Safety Population:** This population consists of all randomized patients who receive at least 1 dose of IP (amifampridine or placebo)
- **Full Analysis Set (FAS):** This population consists of all randomized patients who receive at least 1 dose of IP (amifampridine or placebo) and have at least one post-treatment efficacy assessment.
- **Per Protocol (PP):** This population is a subset of the FAS population, excluding patients with major protocol deviations. The PP population will include all patients who:
 - Have no major protocol deviations or inclusion/exclusion criteria deviations that might potentially affect efficacy, and
 - Patients who took at least 80% of the required treatment doses and remained enrolled for at least 4 days.

Evaluations obtained at the time of discontinuation will be included in the analyses. Patients who discontinue with no post-randomization data will be excluded from all efficacy analyses but will be included in the safety analyses.

13.3 Safety Analysis

Safety analyses will be conducted on the Safety Population. The safety analysis will be descriptive and will be presented using observed data only.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Only TEAEs will be included in the safety analysis. The incidence of TEAEs will be summarized by system organ class, preferred term, relationship to IP, and severity by treatment. Deaths, SAEs, and AEs leading to premature discontinuation will be listed. Vital signs, ECGs, physical examination data, and concomitant medications will also be summarized. Routine laboratory assessments will not be performed. Laboratory evaluations, if performed, will be listed.

13.4 Efficacy Analysis

Efficacy analyses will be conducted on the FAS and PP populations, with the FAS population serving as the primary analysis set. For each efficacy variable with a corresponding assessment at Baseline, Change From Baseline (CFB) will be computed as the post-treatment result minus the Baseline result. The post-treatment result will be the result obtained on Day 4, unless the subject discontinued treatment early, in which case the post-treatment result may be obtained at an earlier time point. For statistical tests, two-sided P values <0.05 will be considered as statistically significant.

Summary statistics for QMG score and the corresponding CFB will be presented by treatment. The analysis of CFB for Total QMG Score is a coprimary efficacy endpoint and analysis will be performed by fitting a fixed effects linear model to the data with CFB as the response. The model will include terms for treatment and QMG at Baseline. The following test comparing the least squares (LS) means will be conducted to evaluate the treatment effect:

$HA,0: LS\text{Mean}QMG(A) = LS\text{Mean}QMG(P) \quad \text{vs.} \quad HA,1: LS\text{Mean}QMG(A) \neq LS\text{Mean}QMG(P),$

where $LS\text{Mean}QMG(A)$ is the QMG LS mean of the amifampridine treatment group and $LS\text{Mean}QMG(P)$ is the QMG LS mean of the placebo treatment group.

The raw scores and CFB for each item of QMG will be summarized by treatment. Between-treatment comparisons with respect to CFB for Right arm outstretched, Left arm outstretched, Right leg outstretched, and Left leg outstretched will be performed using a GLM with terms for treatment, QMG at Baseline and treatment duration (in days).

Summary statistics for SGI score and the corresponding CFB will be presented by treatment. The analysis of CFB for SGI is a coprimary efficacy endpoint and analysis will be performed by fitting a fixed effects linear model to the data with CFB as the response. The model will include terms for treatment and SGI at Baseline. The following test comparing the LS means will be conducted to evaluate the treatment effect:

HB,0: $LSMeanSGI(A) = LSMeanSGI(P)$ vs. HB,1: $LSMeanSGI(A) \neq LSMeanSGI(P)$,

where $LSMeanSGI(A)$ is the SGI LS mean of the amifampridine treatment group and $LSMeanSGI(P)$ is the SGI LS mean of the placebo treatment group.

A sensitivity analysis of the coprimary endpoints will be conducted to evaluate the patterns of early treatment discontinuation. For each coprimary endpoint, a randomization test will be conducted to determine if the results from the primary analysis are supported. The randomization test is an alternative to a full permutation, and will evaluate the fixed effects model specified above using permutations of the treatment group assignments. If early discontinuations are not associated with treatment, then it is expected that the p-value resulting from the randomization test will yield the same statistical interpretation as the p-value resulting from the primary analysis.

The proportion of patients with at least 20% increase in average time for 3TUG will be summarized by treatment and analyzed using Fisher's Exact Test. The assessment of the Patient's Most Bothersome Symptom will be summarized by treatment and analyzed using a Wilcoxon Rank Sum Test.

13.5 Changes in the Conduct of the Study or Planned Analyses

Any change in study conduct considered necessary by the Investigator will be made only after consultation with Catalyst, who will then issue a formal protocol amendment to implement the change. The only exception is when an Investigator considers that a patient's safety is compromised without immediate action. In these circumstances, immediate approval of the IRB/IEC/REB must be sought, and the Investigator should inform Catalyst within 2 working days after the emergency occurs.

14 COMPENSATION, INSURANCE AND INDEMNITY

There will be no charge to study patients to be in this study. Catalyst will pay all costs of test, procedures, and treatment that are part of this study (as included in the site budget). In addition, after IRB/IEC/REB approval, Catalyst will pay the cost of travel, lodging and meals for study duration. Catalyst will not pay for any hospitalizations, tests, or treatment for medical problems of any sort, whether or not related to the study patient's disease that are not part of this study. Costs associated with hospitalizations, test, and treatments should be billed and collected in the way that such costs are usually billed and collected.

The Investigator should contact Catalyst immediately upon notification that a study patient has been injured by the IP or by procedures performed as part of the study. Any patient who experiences a study-related injury should be instructed by the Investigator to seek medical treatment at the closest medical treatment facility if necessary. The patient should be given the name of a person to contact to seek further information about, and assistance with, treatment for study-related injuries. The treating physician should bill the patient's health insurance company or other third party payer for the cost of this medical treatment. To the extent a patient has reasonably followed the Investigator's instructions and attempted to comply with study procedures, Catalyst will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, Catalyst is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. If this is the case, Catalyst will comply with the law.

15 CASE REPORT FORMS AND SOURCE DOCUMENTS

The CRO data management vendor, or designees, will perform all data management activities, including the writing of a data management plan outlining the systems and procedures to be used.

Study data will be captured on CRFs and will be verified to the source data, which necessitates access to all original recordings, laboratory reports, and patient records. In addition, all source data should be attributable (signed and dated). The Investigator must therefore agree to allow direct access to all source data. Patients must also allow access to their medical records, and patients will be informed of this and will confirm their agreement when giving informed

consent. The Investigator must review and sign the completed CRF casebook to verify its accuracy.

16 STUDY MONITORING AND AUDITING

Qualified individuals approved and/or designated by Catalyst will monitor all aspects of the study according to GCP and SOPs for compliance with applicable government regulations. The Investigator agrees to allow these monitors direct access to the clinical supplies, dispensing, and storage areas and to the clinical files, including original medical records, of the study patients, and, if requested, agrees to assist the monitors. The Investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by Catalyst or its designees.

Members of Catalyst's GCP Compliance Department or designees may conduct an audit of a clinical site at any time before, during, or after completion of the study. The Investigator will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other regulatory agencies may also conduct an audit of the study. If informed of such an inspection, the Investigator should notify Catalyst immediately. The Investigator will ensure that the auditors have access to the clinical supplies, study site facilities, original source documentation, and all study files.

17 RETENTION OF RECORDS

The Investigator must retain all study records required by Catalyst and by the applicable regulations in a secure and safe facility. The Investigator must consult a Catalyst representative before disposal of any study records, and must notify Catalyst of any change in the location, disposition or custody of the study files. The Investigator/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g. patient charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until (1) there are no pending or contemplated marketing applications in an ICH region or (2) at least 2 years have elapsed since the formal

discontinuation of clinical development of the IP. The Investigator/institution should retain patient identifiers for at least 15 years after the completion or discontinuation of the study. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by a Catalyst agreement. Catalyst must be notified and will assist with retention should Investigator/institution be unable to continue maintenance of patient files for the full 15 years. It is the responsibility of Catalyst to inform the Investigator /institution as to when these documents no longer need to be retained.

18 USE OF INFORMATION AND PUBLICATION

Catalyst recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in any Clinical Trial Agreement.

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20 SIGNATURE PAGE

Protocol Title: A Phase 3, Double-blind, Placebo-controlled, Randomized, Parallel-Group Study to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with Lambert-Eaton Myasthenic Syndrome (LEMS)

Protocol Number: LMS-003

I have read the forgoing protocol and agree to conduct this study as outlined. I agree to conduct the study in compliance with all applicable regulations and guidelines, including ICH E6, as stated in the protocol, and other information supplied to me.

Investigator Signature

Date

Printed name: _____

Accepted for Catalyst:

On behalf of Catalyst, I confirm that Catalyst, as a sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the Investigator is informed of all relevant information that becomes available during the conduct of this protocol.

Medical Monitor Signature

Date

Printed name: Gary Ingenito, MD, PhD
Chief Medical Officer
Catalyst Pharmaceuticals, Inc.

Appendix 1 Quantitative Myasthenia Gravis Testing Form

<u>TEST ITEMS WEAKNESS</u>	<u>NONE</u>	<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>	<u>SCORE</u>
GRADE	0	1	2	3	
Double vision (lateral gaze) Sec.	60	11-59	1-10	Spontaneous	
Ptosis (upward gaze) Sec.	60	11-59	1-10	Spontaneous	
Facial Muscles	Normal lid closure	Complete, weak, some	Complete, without resistance	Incomplete	
Swallowing 4 oz. Water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing Choking or nasal regurgitation	Cannot swallow (test not attempted)	
Speech following counting aloud from 1-50 (onset of dysarthria)	None at #50	Dysarthria at #30-49	Dysarthria at #10-29	Dysarthria at #9	
Right arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	
Left arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	
Forced vital capacity	≥80%	65-79%	50-64%	<50%	
Rt hand grip: male (Kg) :	≥45 ≥30	15-44 10-29	5-14 5-9	0-4 0-4	
Left hand grip: male (Kg) :	≥35 ≥25	15-34 10-24	5-14 5-9	0-4 0-4	
Head, lifted (45%, supine) Sec.	120	30-119	1-29	0	
Right leg outstretched (45-50%, supine) Sec.	100	31-99	1-30	0	
Left leg outstretched (45-50%, supine) Sec.	100	31-99	1-30	0	

Appendix 2 Subject Global Impression (SGI)

The SGI will be assessed at the protocol-specified time points (see [Table 3](#)) by the patient.

Using the 7-point scale below, rate your impression of the effects of the study medication during the preceding 3 days on your physical well being.

1=Terrible

2= Mostly dissatisfied

3= Mixed

4=Partially satisfied

5= Mostly satisfied

6= Pleased

7= Delighted

Appendix 3 Clinical Global Impression-Improvement (CGI-I)

The CGI-I will be used to capture the Investigator's global impression of the patient's improvement at the end of treatment (Day 4), compared to their condition at the time of randomization (Day 0).

The Investigator will complete the 7-point CGI-I, based on changes in symptoms, behavior, and functional abilities, at the protocol-specified time points.

Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment. Compared to the patient's condition at Day 0, how much has it changed?

- 1 = Very much improved
- 2 = Much improved
- 3 = Minimally improved
- 4 = No change
- 5 = Minimally worse
- 6 = Much worse
- 7 = Very much worse

Appendix 4 Timed Up and Go (TUG) Test

Equipment: Stopwatch, Standard Chair with armrests and seat height approximately 44 cm (17 inches) and arm rest height approximately 65 cm (26 inches), Measured distance of 3 meters (9 feet 10 inches).

Patient Instructions given by the evaluator:

“Sit in the chair with your back resting on the back of the chair and hands on the armrests. At the end of the test mat in front of you is a green light. When you see the green light turn on, I want you to get up from the chair. You should use the arms of the chair to assist in standing up or sitting down from the chair. Walk forward as quickly as you feel comfortable until you reach the orange area on the floor marking the end of the course. You need to be in the orange area with both feet, turn around, walk back to the chair, turn around and sit down completely in the chair, touching your back to the back of the chair. Immediately repeat the course I have just explained to you two more times. Therefore, you will complete the course a total of three times without resting between each time that you do the course.”

“I will record the time it takes you to complete the course three times, with the ending time occurring when you sit down in the chair for the third time. You may not use the wall for support. Please try to complete the course three times without resting between each time, if possible.”

“We will begin in a moment. Please focus on the light at the end of the course and listen for the beep. Begin immediately upon hearing the beep and seeing the light. Thank you.”

Evaluator instructions:

The timing, gait, and progress in this test will be recorded automatically by the Prokinetics software, both electronically by the sensor mat and by video camera. Ensure that the subject's back is touching the back of the chair at the beginning and end of each cycle of the course. Ensure that the subject's wear their regular footwear for the test and that they wear the same footwear each time the test is conducted. Refer to past records to ensure the subject's footwear has not changed between days. The subject may use a walking assistive device (cane or walker) if that is their usual and normal practice for walking. If a walking assistive device

is used, record the type of device in the source documents. This device should be used for each evaluation. Subject's may not be assisted by another person during this test. If the subject's become fatigued while walking, they may stop and rest, but should not sit down. Any comments or question directed to the subject during the test should be for safety reasons only and be non-directive. For example, "Are you ok?". Remember that the entire test is recorded by video.

Appendix 5 Most Bothersome Symptom Scale

Question 1:

Before treatment for LEMS or while off of medication, what was your most bothersome symptom and how would you rate it?

0 = Not at all bothersome

1 = Bothered me a little

2 = Bothered me some

3 = Bothered me a lot

Question 2:

After treatment with the study medication, how would you rate the most bothersome symptom that you previously identified, during the last 24 hours?

0 = Not at all bothersome

1 = Bothers me a little

2 = Bothers me some

3 = Bothers me a lot

Appendix 6 Protocol Amendment 1

PURPOSE: The purpose of this amendment is as follows:

Risk: these administrative changes provide clarity, adding no additional risk to the patient.

MODIFICATIONS TO PROTOCOL:

- **Bold and underlined text:** Changed Text
- **~~Bold and strike through text:~~** Deleted Text
- ***Bold and italicized text:*** Added Text

On Page 1, on the header changed text.

Amendment 1

On Page 1, under Study Title, deleted and added text.

~~Two period Two treatment Crossover~~

Parallel- Group

On Page 1, under Study Design, deleted and added text.

~~Two period Two treatment Crossover~~

Parallel- Group

On Page 1, under Date of Protocol added text.

Date of Amendment 1: 18 September 2016

On Page 3, under Title of Study, deleted text and added text.

~~Two period Two treatment Crossover~~

Parallel- Group

On Page 3, under Study Design and Plan, deleted and added text.

~~Two period Two treatment Crossover~~

Parallel- Group

On Page 3, under Study Design and Plan, deleted up to 24 males and added added 28.

The study is planned to include ~~up to 24~~ approximately 28 male and female patients.

On Page 3, under Study Design and Plan, deleted 8 days and added 5 days (Day 0 through Day 4).

The planned duration of participation for each patient is **8 5 days (Day 0 through Day 4), excluding the screening period, which can last up to 7 days.**

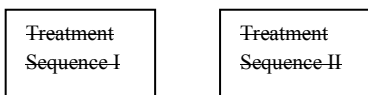
On Page 4, under Study Design and Plan, deleted and added text.

Treatment Sequence Group.

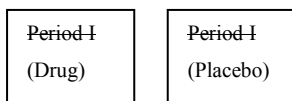
On Page 4, under Study Design and Plan, deleted and added text.

Amifampridine phosphate (at the patient's optimal dose) or placebo will be dispensed by the site pharmacist, according to the randomization schedule, to begin *with the next dose after all Day 0 assessments are completed and continued for the 4 days of Period 1.* Following Period 1, patients will receive the treatment not received during Period 1, during double-blind Period 2, for 4 days (Days 5-8). After completion of Period 2 the study, patients will be eligible for expanded access treatment program with open-label amifampridine phosphate.

On Page 4, on figure, deleted text boxes.



On Page 4, on figure, changed text boxes.



On Page 4, under Screening, deleted text.

They can be randomized if on a stable dose and frequency of amifampridine phosphate for at least 1 week before being randomized. to a Treatment Sequence.

On Page 4, under Screening, deleted and added text.

Period 1 Treatment (Days 1-4) (+1 day)

On Page 4, under Treatment (Days 1-4) (+1 day), deleted and added text.

Patients will be randomized (1:1 ratio) on the last day of the screening period (Day 0) to either ~~Treatment Sequence I or II and commence Period 1 for the respective Treatment Sequence~~ amifampridine phosphate or placebo. Beginning with the next dose after all Day 0 assessments are completed ~~on Day 1 of Period 1~~, the patient will take, under double-blind conditions, either amifampridine phosphate tablets or placebo tablets ~~for through~~

Day 4 days, with a clinic visit on the last day of Period 1 (Day 4) for assessments (Table 3). Any unused portion of dispensed drug will be returned before dispensing drug for Period 2.

On Page 4, under Treatment (Days 1-4) (+1 day), deleted paragraph.

Period 2 (Days 5-8) (+1 day)

~~After completion of Period 1, patients will receive the blinded study appropriate medication/placebo for Period 2 during Study Days 5-8 as per their randomized Treatment Sequence. A clinic visit will occur at the end of Period 2 (Day 8) for final study assessments (Table 3).~~

On Page 4, under Number of Patients Planned deleted and added text.

~~Up to 24~~ Approximately 28 patients to enroll in the study.

On Page 5, under Investigational Product(s), Dose Route and Regimen, deleted text.

Amifampridine phosphate tablets are to be taken orally by mouth with food.

On Page 6, under Sample Size Determination deleted and added text.

For Change From Baseline in QMG Scores, a between-treatment difference of -2.83.5 and a standard deviation at most 3.07, as observed in LSM-002, a sample size of at least 11 24 patients per sequence will provide power of at least 80% for a 0.05 level test using the two-period, two-treatment crossover design. Similarly, for Change From Baseline in SGI Scores, a between-treatment difference of -2.1 and a standard deviation at most 2.42, as observed in LSM-002, a sample size of at least 1226 patients per sequence will provide power of 80% for a 0.05 level test using the two-period, two-treatment crossover design. Thus a total sample size of 24 26 patients, equally randomized to the two treatments sequences, will provide power of at least 80% for each of the two co-primary endpoints.

On Page 7, under Efficacy Analysis deleted text.

Each of the efficacy variables, as well as Change From Baseline (CFB) if appropriate, will be summarized by treatment and period. P values <0.05 will be considered as statistically significant.

On Page 7, under Efficacy Analysis deleted and added text.

~~The between-treatment comparisons with respect to the CFB in QMG total scores, and SGI will be performed using a two-period, two-treatment crossover design. The 95%~~

~~confidence interval (CI) based on this model will be presented for the difference in the Least Squares (LS) means for each of these analyses.~~ *Summary statistics for QMG score and the corresponding CFB will be presented by treatment. The analysis of CFB for Total QMG Score is a coprimary efficacy endpoint and analysis will be performed using analysis of covariance (ANCOVA) with QMG at Baseline as the only covariate.*

On Page 7, under Efficacy Analysis deleted and added text.

~~The scores for each item of QMG will be summarized by treatment. and period and between-treatment comparisons with respect to scores for Right arm outstretched, Left arm outstretched, Right leg outstretched, and Left leg outstretched will be performed using a two-period, two-treatment crossover design with a multinomial logistic regression model.~~ *ANCOVA with the corresponding assessment at Baseline as the only covariate.*

On Page 7, under Efficacy Analysis deleted and added text.

Summary statistics for SGI and the corresponding CFB will be presented by treatment. The analysis of CFB for SGI is a coprimary efficacy endpoint and analysis will be performed using ANCOVA with SGI at Baseline as the only covariate.

~~The proportion of patients with at least 20% increase in average time for 3TUG and assessment of the Patient's Most Bothersome Symptom will be summarized by treatment and period and analyzed using a nonparametric approach.~~

On Page 10, in table of contents, added text.

20. Protocol signature page

On Page 28, under Overall Study Design and Plan, deleted and added text.

~~This randomized (1:1), double-blind, placebo-controlled, two-period, two-treatment crossover~~ *parallel-group study is designed to evaluate the efficacy and safety of amifampridine phosphate in patients diagnosed with LEMS.*

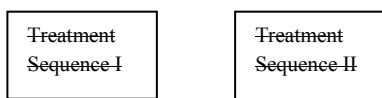
On Page 28, under Overall Study Design and Plan, deleted and added text.

~~The study is planned to include up to 24~~ *approximately 28 male and female patients. The planned duration of participation for each patient is 8 5 days, excluding the screening period, which can last up to 7 days.*

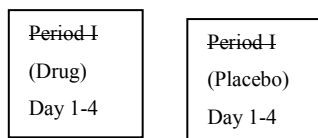
On Page 28, under Overall Study Design and Plan, deleted and added text.

Those patients successfully satisfying all screening criteria will be randomized to a ~~Treatment Sequence~~*treatment group*. Amifampridine phosphate (at the patient's optimal dose) or placebo will be dispensed by the site pharmacist, according to the randomization schedule, to begin *with the next dose after all Day 0 assessments are completed and continued for the 4 days of Period 1*. ~~Following Period 1, patients will receive the treatment not received during Period 1, during double-blind Period 2, for 4 days (Days 5-8).~~ After completion of ~~Period 2~~*the study*, patients will be eligible for expanded access treatment program with open-label amifampridine phosphate.

On Page 29, on figure, deleted text boxes.



On Page 29, on figure, changed text boxes.



On Page 29, under screening deleted and added text.

Patients receiving amifampridine phosphate treatment for LEMS, and meeting the inclusion and exclusion criteria are eligible to participate in this study. They can be randomized ~~into Period 1~~ if on stable dose and frequency of amifampridine phosphate for at least 1 week before being randomized to a ~~Treatment Sequence~~*treatment*.

On Page 29, under Treatment (Days 1-4) (+1 day), deleted and added text.

Patients will be randomized (1:1 ratio) on the last day of the screening period (Day 0) to either ~~Treatment Sequence I or II and commence Period 1 for the respective Treatment Sequence~~*amifampridine phosphate or placebo*. Beginning with the next dose after all Day 0 assessments are completed ~~on Day 1 of Period 1~~, the patient will take, under double-blind conditions, either amifampridine phosphate tablets or placebo tablets ~~for through Day 4 days~~, with a clinic visit on the last day ~~of Period 1~~(Day 4) for assessments ([Table 3](#)). Any unused portion of dispensed drug will be returned ~~before dispensing drug for Period 2~~.

On Page 29, under Treatment (Days 1-4) (+1 day), deleted and added text.

Period 2 (Days 5-8) (+1 day)

~~After completion of Period 1, according to the randomization schedule, patients will receive the blinded study appropriate medication/placebo for Period 2 for 4 days (Day 5-8). Patients begin taking investigational material for Period 2 on the morning of Day 5. A clinic visit will occur at the end of Period 2 (Day 8) for final study assessments (Table 3).~~

During all phases of the study, safety and efficacy assessments will be made as detailed in the Schedule of Assessments in Table 3.

On Page 30, on Table 3, deleted text

Period 1

On Page 30, on Table 3, added text.

Blinded IP dispense

On Page 30, on Table 3, deleted row.

IP administration

On Page 30, on Table 3, deleted column 5.

Period 2**Days 5-8****Day 8****(+1 d)**

On Page 30, on Table 3, added text.

Urine sample for amifampridine level²

On Page 30, on Table 3, deleted and added text.

Pregnancy test – urine^{2,3}

On Page 30, on Table 3 between Urine sample for amifampridine level² and Day 4(+1d) deleted text.

X⁴

On Page 30, under Table 3 deleted text.

³Drug dispensed for Period 2, at end of Period 1

On Page 30, under Table 3 deleted and added text.

³Urine specimen for amifampridine level will be collected on Days 3 and 4, 7 and 8

On Page 30, under Table 3, deleted text.

~~²Women of child-bearing potential~~³²*Urine specimen for amifampridine level will be collected on Days 3 and 4*

On Page 30, under Table added text.

³*Women of child-bearing potential*

On Page 32, under Removal of Patients from Treatment or Assessment, deleted and added text.

In the event that the patient's LEMS symptoms worsen to a clinically significant level, in the opinion of the Investigator, the patient may be placed on open-label amifampridine phosphate, and Early ~~Termination~~ *Discontinuation* assessments should be performed as described for ~~Period 2~~, Day 8 4 (Table 3).

On Page 33, under Patient Identification and Randomization, deleted and added text.

Randomization will be across sites to maintain the 1:1 ratio of drug: placebo assignment. The assignments to treatment (amifampridine phosphate or placebo) will be based on a computer-generated randomization code. Study site Pharmacy will obtain the ~~Treatment Sequence~~*treatment group* for the subject to be enrolled in ~~Period 1~~ at the time of randomization (Day 0).

On Page 35, under Directions for Administration, deleted text.

30 mg to 80 mg, divided into doses taken 3 to 4 times per day ~~taken with food (e.g. breakfast, lunch, dinner, and snack before bed)~~

On Page 36, under Method of Assigning Patients to Treatment Groups, deleted and added text.

Patients will be randomized Day 0 to either ~~Treatment Sequence I or II~~, *treatment group* in a 1:1 ratio. IP will be administered ~~within Period 1 and Period 2~~ under double-blind conditions ~~for each Treatment Sequence~~ such that neither the Investigator nor patient knows if they are taking placebo or amifampridine phosphate.

On Page 37, Treatment Compliance, deleted text.

Patients will be instructed to return all IP containers and remaining study medication at ~~each~~ *the* study clinic visit.

On Page 41, under Efficacy Variables, added text.

Exploratory Efficacy Variables

On Page 41, section 8.7.4, deleted text.

The Timed Up and Go (TUG) is a functional mobility test that requires a subject to stand up from ~~an 18 inch~~ straight-backed armchair, walk 3 meters, turn around, walk back, and sit down in the chair.

On Page 42, under 8.7.5, deleted and added text.

The evaluation consists of 2 questions, the first is to identify before treatment or while off medication, what the patient perceived as their most bothersome symptom ***and the level to which it bothered them, on a 4 point scale.*** ~~The second question is the evaluation of that symptom during each of the double-blind treatment periods.~~ ***Following blinded treatment with study medication, the patient is asked to evaluate how much the previously identified symptom bothered them during the prior 24 hours, on the same 4 point scale.***

On Page 43, under Adverse Events, deleted and added text.

The study period during which all serious and non-serious AEs will be reported begins after informed consent is obtained and through the last visit of Period 2 on Study Day 8 4

On Page 43, under Adverse Events, deleted and changed text.

(refer to Section ~~11.2~~ 9.2 for SAE definition).

On Page 50, under Randomization Visit (Study Day 0) deleted and added word.

Patients who are deemed eligible will be dispensed double-blind study medication (amifampridine phosphate or placebo tablets) on Study Day 0, according to the treatment ~~sequence~~ group to which they are randomized. The patient's open-label amifampridine must be collected ~~and only enough pills to complete usual dosing on Day 0 provided.~~ Patients must stop their open-label amifampridine and will start to take the blinded study medication the next morning (Study Day 1) beginning with the next scheduled dose after all assessments on open-label medication have been completed.

On Page 50, under Table, deleted and added text.

Patients must be instructed that they are not to take any doses of their prior, open-label amifampridine during ~~either Period 1 or Period 2~~ the study and not to change pyridostigmine dose or schedule.

On Page 50, under End of Treatment (Study Day 4), titled changed

End of Period 1 Treatment (Study Day 4)

On Page 50, under End of Treatment (Study Day 4), deleted and added text.

Patients will take their blinded study medication on Days 1-3 ~~of Period 1.~~ On Day 4, a dose of blinded study medication must be administered by the site study personnel. This is the same medication that the patient has been taking on Days 1-3 ~~of Period 1.~~

On Page 50, under End of Treatment (Study Day 4), deleted and added text.

For example, If the patient took their second dose of amifampridine in the clinic on Day 0 and had assessments started 40 minutes later, then on Day 4 and 8, that patient should be assessed after taking their second dose of medication in the clinic, starting 40 minutes after the dose.

On Page 51, under End of Treatment (Study Day 4), deleted and added text.

A urine sample, to determine amifampridine level, should be collected on Day 2-3 or Period 1, and on Day 4, before study personnel give the dose of blinded medication.

On Page 51, under Table deleted text.

The patient should be given back only enough of the Period 1 study medication to complete dosing for that day (Day 4).

On Page 51, deleted paragraph and section 11.4.

~~A new container of blinded study medication for Period 2 will be given to the patient at the end of the assessments. Blinded study medication for Period 2 is to be taken beginning the next morning, Study Day 5, after completing all Day 4 medication.~~

11.4 End of Period 2 (Study Day 8)

~~Patients will take their blinded study medication on Days 5-7 of Period 2. On Day 8, blinded study medication will be administered by the site study personnel. This is the same medication that the patient has been taking on Days 5-7 of Period 2. The assessments listed below will be performed following either the second, third, or fourth dose of medication to be taken on Day 4, and this should be the same specific dose after which assessments on Day 0 were subsequently performed.~~

~~Safety assessments (vital signs and AEs/SAEs) should be performed before study personnel give the dose of blinded medication. Concomitant medications should be reviewed for any changes.~~

Assessment	Start Time After Dose* (+ 10 minutes unless otherwise specified)
SGI	40 minutes
Patient most bothersome symptom, Question 2	Following SGI
QMG	Following patient symptom evaluation
CGI-I (compared to Day 0 and Day 4)	Following QMG
3TUG	Following CGI-I

*Administration of medication represents Time 0 (minutes)

~~The container of blinded study medication dispensed on Study Day 4 must be returned to study personnel and the IP Accountability form completed to determine if the blinded study medication doses were taken. Sufficient tablets should be returned to the patient to complete any remaining doses for Day 8.~~

On Page 52, under Early Discontinuation Visit, deleted text.

- CGI-I (compared to Day 0 and Day 4, based upon the time of discontinuation)

On Page 52, under Determination of Sample Size, deleted and added text.

For Change From Baseline in QMG Scores, a between-treatment difference of -2.83.5 and a standard deviation at most 3.07, as observed in LSM-002, a sample size of at least 11 24 patients per sequence will provide power of at least 80% for a 0.05 level test using the two-period, two-treatment crossover design. Similarly, for Change From Baseline in SGI Scores, a between-treatment difference of -2.1 and a standard deviation at most 2.42, as observed in LSM-002, a sample size of at least 12 26 patients per sequence will provide power of 80% for a 0.05 level test using the two-period, two-treatment crossover design. Thus a total sample size of 24 26 patients, equally randomized to two treatment sequences, will provide power of at least 80% for each of the two co-primary endpoints.

On Page 53, under Efficacy Analysis, deleted and added text.

Each of the efficacy variables, as well as Change From Baseline (CFB) if appropriate, will be summarized by treatment **and period**.

~~QMG total scores and SGI are co-primary endpoints. The between-treatment comparisons with respect to the CFB in QMG total scores and SGI, will be performed using a two-period, two-treatment crossover design. The 95% confidence interval (CI) based on this model will be presented for the difference in the Least Squares (LS) means for each of these analyses. Summary statistics for QMG score and SGI, and the corresponding CFB, will be presented by treatment. The analysis of CFB for Total QMG Score and SGI are coprimary efficacy endpoints and analysis will be performed using ANCOVA with QMG or SGI at Baseline as the only covariate, respectively.~~

The scores for each item of QMG will be summarized by treatment. ~~and period and~~ ~~Between-treatment comparisons with respect to scores for Right arm outstretched, Left arm outstretched, Right leg outstretched, and Left leg outstretched will be performed using a two-period, two-treatment crossover design with a multinomial logistic regression model.~~ *ANCOVA with the corresponding assessment at Baseline as the only covariate.*

The proportion of patients with at least 20% increase in average time for 3TUG will be summarized by treatment ~~and period~~ and analyzed using a ~~nonparametric approach~~ *Fisher's Exact Test*. The assessment of the Patient's Most Bothersome Symptom will be summarized by treatment ~~and period~~ and analyzed using a ~~nonparametric approach~~ *Wilcoxon Rank Sum Test*.

On Page 62, Signature page added.

On Page 65, under Appendix 3, deleted and added text.

The CGI-I will be used to capture the Investigator's global impression of the patient's improvement at the end of ~~each double-blind~~ treatment **(Day 4) period**, compared to their condition at the time of randomization **(Day 0)**.

On Page 66, Appendix 4, deleted and added text.

I will record the time it takes you to complete the course three times, with the ending time occurring when your ~~back touches the back of~~ **sit down in** the chair for the third time.

Appendix 7 Protocol Amendment 2

PURPOSE: The purpose of this amendment is as follows:

Risk: these administrative changes provide clarity, adding no additional risk to the patient.

MODIFICATIONS TO PROTOCOL:

- **Bold and underlined text:** Changed Text
- **~~Bold and strike through text:~~** Deleted Text
- ***Bold and italicized text:*** Added Text

On Page 1, on the header added text.

Amendment 2

On Page 2, under Emergency Contact Information deleted and added text.

~~Richard Erwin~~ *Adriana Manari*

~~Executive Director~~ *Clinical Trial Manager*

~~Ext. 130 117~~

~~rerwin@catalystpharma.com~~ *amanari@catalystpharma.com*

On Page 5, under Criteria for Inclusion and Exclusion, deleted and added text.

1. Male or female ≥ 18 years of age ***with LEMS*** and currently receiving ***a stable dose of*** amifampridine phosphate for ~~LEMS~~ ***at least 7 days.***

On Page 5, under Criteria for Inclusion and Exclusion, added text.

8. ***Patients who cannot discontinue immunomodulatory treatment (e.g. mycophenolate, azathioprine, cyclosporine) within 3 weeks before screening.***

On Page 7, under Efficacy Analysis deleted and added text.

~~Each of the efficacy variables, as well as Change From Baseline (CFB) if appropriate, will be summarized by treatment~~ ***For each efficacy variable with a corresponding assessment at Baseline, Change From Baseline (CFB) will be computed as the post-treatment result minus the Baseline result. The post-treatment result will be the result obtained on Day 4, unless the subject discontinued treatment early, in which case the post-treatment result may be obtained at an earlier time point. For statistical tests, two-sided P values < 0.05 will be considered as statistically significant.***

Summary statistics for QMG score and the corresponding CFB will be presented by treatment. The analysis of CFB for Total QMG Score is a coprimary efficacy endpoint and analysis will be performed ~~using analysis of covariance (ANCOVA)~~ **by fitting a general linear fixed effects linear model (GLM) to the data with CFB as the response. The model will include terms for treatment, with and; QMG at Baseline and treatment duration (in days) as the only covariate. A test comparing least squares (LS) means will be conducted to evaluate the treatment effect.**

The *raw* scores, and CFB for each item of QMG will be summarized by treatment. Between-treatment comparisons with respect to CFB for Right arm outstretched, Left arm outstretched, Right leg outstretched, and Left leg outstretched will be performed using ~~ANCOVA~~ **a fixed effects linear model with terms for treatment and QMG at Baseline. with the corresponding assessment at Baseline as the only covariate.**

Summary statistics for SGI *score* and the corresponding CFB will be presented by treatment. The analysis of CFB for SGI is a coprimary efficacy endpoint and analysis will be performed **by fitting a GLM fixed effects linear model to the data with CFB as the response. The model will include terms for treatment and; SGI at Baseline and treatment duration (in days) using ANCOVA with SGI at Baseline as the only covariate.**

On Page 29, under 8.1 Overall Study Design and Plan added text.

Patients will have been receiving unblinded drug treatment **in the expanded access program (EAP-001)**, after which blinded treatment effect will be assessed for continuation or cessation of drug.

On Page 30, under Screening added text.

They can be randomized if on stable dose and frequency of amifampridine phosphate for at least 1 week before being randomized to a treatment. **Screening and randomization (Day 0) may be combined into a single visit.**

On Page 33, under 8.2.1 Inclusion Criteria deleted and added text.

1. Male or female ≥ 18 years of age **with LEMS** and currently receiving **a stable dose of amifampridine phosphate for LEMS at least 7 days.**

On Page 33, under 8.2.1 Inclusion Criteria deleted and added text.

5. If receiving permitted oral immunosuppressants (prednisone or other corticosteroid, **azathioprine, mycophenolate**), a stable dose is required for at least 30 days prior to randomization and throughout the study.

On Page 33, under 8.2.2 Exclusion Criteria deleted and added text.

3. Active brain metastases.

3.4. *Unable to ambulate*

4.5. *Pregnant or lactating females.*

6. Any other condition which, in the opinion of the investigator, might interfere with the patient's participation in the study or confound the assessment of the patient.

5.7. *Patients who cannot discontinue immunomodulatory treatment (e.g. mycophenolate, azathioprine, cyclosporine) within 3 weeks before screening.*

On Page 35, under 8.2.4 Patient Identification and Randomization deleted and added text.

Upon signing of the ICF, subjects will be assigned an ID composed of a 2 digit site number and a ~~3-or-4~~ 2 digit subject number.

On Page 40, on title Table 4. Medications Prohibited Before and During Study, added text.

Table 5. Medications Prohibited *Before and* During Study

On Page 40, under Table 4. Medications Prohibited Before and During Study, added text.

Immunomodulatory treatment (e.g. azathioprine, mycophenolate, *cyclosporine*) within 3 weeks before Screening

On Page 41, under 8.6.3 Clinical Laboratory Assessments added text.

The procedure involves collecting tubes of blood which is then incubated with a variety of antibodies directed towards circulating tumor cells. Additional analysis of identified cells may then be performed. *Follow-up screening will be performed by expanded access clinical sites.*

On Page 46, under Table 5 added text.

The Investigator should review the AE Log for the patient, from the EAP-001 expanded access program. Any ongoing/open/unresolved AEs will be transcribed to the LMS-003 study AE Log. At the end of patient's participation in the LMS-003 study, the AE Log should be provided to the expanded access program site, so that the expanded access site can update their AE Log with any changes.

On Page 52, under 11.3 End of Treatment (Study Day 4) added text.

A urine sample, to determine amifampridine level, should be collected on Day 3 (*after patient has taken a dose of blinded medication*), and on Day 4, before study personnel give the dose of blinded medication.

On Page 53, under table deleted text.

~~The patient should be given back only enough of the study medication to complete dosing for that day (Day 4).~~

On Pages 55 and 56, under 13.4 Efficacy Analysis deleted and added text.

~~Each of the efficacy variables, as well as Change From Baseline (CFB) if appropriate, will be summarized by treatment. P values <0.05 will be considered as statistically significant.~~

~~Summary statistics for QMG score and SGI, and the corresponding CFB, will be presented by treatment. The analysis of CFB for Total QMG Score and SGI are coprimary efficacy endpoints and analysis will be performed using ANCOVA with QMG or SGI at Baseline as the only covariate, respectively.~~

~~The scores for each item of QMG will be summarized by treatment. Between-treatment comparisons with respect to scores for Right arm outstretched, Left arm outstretched, Right leg outstretched, and Left leg outstretched will be performed using ANCOVA with the corresponding assessment at Baseline as the only covariate.~~

Efficacy analyses will be conducted on the FAS and PP populations, with the FAS population serving as the primary analysis set. For each efficacy variable with a corresponding assessment at Baseline, Change From Baseline (CFB) will be computed as the post-treatment result minus the Baseline result. The post-treatment result will be the result obtained on Day 4, unless the subject discontinued treatment early, in which case the post-treatment result may be obtained at an earlier time point. For statistical tests, two-sided P values <0.05 will be considered as statistically significant.

Summary statistics for QMG score and the corresponding CFB will be presented by treatment. The analysis of CFB for Total QMG Score is a coprimary efficacy endpoint and analysis will be performed by fitting a ~~general linear model (GLM)~~ fixed effects linear model to the data with CFB as the response. The model will include terms for treatment, QMG at Baseline and ~~treatment duration (in days)~~. The following test comparing the least squares (LS) means will be conducted to evaluate the treatment effect:

$H_{A,0}: LS\text{Mean}_{QMG}(A) = LS\text{Mean}_{QMG}(P)$ vs. $H_{A,1}: LS\text{Mean}_{QMG}(A) \neq LS\text{Mean}_{QMG}(P)$,

where $LS\text{Mean}_{QMG}(A)$ is the QMG LS mean of the amifampridine treatment group and $LS\text{Mean}_{QMG}(P)$ is the QMG LS mean of the placebo treatment group.

The raw scores and CFB for each item of QMG will be summarized by treatment.

Between-treatment comparisons with respect to CFB for Right arm outstretched, Left arm

outstretched, Right leg outstretched, and Left leg outstretched will be performed using a GLM with terms for treatment, QMG at Baseline and treatment duration (in days).

Summary statistics for SGI score and the corresponding CFB will be presented by treatment. The analysis of CFB for SGI is a coprimary efficacy endpoint and analysis will be performed by fitting a ~~GLM~~ fixed effects linear model to the data with CFB as the response. The model will include terms for treatment and; SGI at Baseline ~~and treatment duration (in days)~~. The following test comparing the LS means will be conducted to evaluate the treatment effect:

$H_{B,0}: LS\text{Mean}_{SGI}(A) = LS\text{Mean}_{SGI}(P)$ vs. $H_{B,1}: LS\text{Mean}_{SGI}(A) \neq LS\text{Mean}_{SGI}(P)$,

where $LS\text{Mean}_{SGI}(A)$ is the SGI LS mean of the amifampridine treatment group and $LS\text{Mean}_{SGI}(P)$ is the SGI LS mean of the placebo treatment group.

A sensitivity analysis of the coprimary endpoints will be conducted to evaluate the patterns of early treatment discontinuation. For each coprimary endpoint, a randomization test will be conducted to determine if the results from the primary analysis are supported. The randomization test is an alternative to a full permutation, and will evaluate the fixed effects model specified above using permutations of the treatment group assignments. If early discontinuations are not associated with treatment, then it is expected that the p-value resulting from the randomization test will yield the same statistical interpretation as the p-value resulting from the primary analysis.

On Page 69, under Appendix 4 Timed Up and Go (TUG) Test deleted and added text.

Walk forward as quickly as you feel comfortable until you ~~pass the piece of tape~~reach the orange area on the floor marking the end of the course. ~~Cross the tape~~You need to be in the orange area with both feet, turn around, walk back to the chair, turn around and sit down completely in the chair, touching your back to the back of the chair.