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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL AND STATISTICAL REVIEW

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Reviewer Name(s)	Veneeta Tandon Junshan Qiu
Review Completion Date	11/28/18
Established/Proper Name	Amifampridine Phosphate
(Proposed) Trade Name	FIRDAPSE
Applicant	Catalyst Pharmaceutical Inc.
Dosage Form(s)	Tablet, 10 mg
Applicant Proposed Dosing Regimen(s)	Starting dose (b) (4) as TID to a maximum of 80 mg/day
Applicant Proposed Indication(s)/Population(s)	(b) (4) treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults 18 years of age or older.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

Reference ID: 4355903

Clinical and Statistical Review
Veneeta Tandon
Junshan Qiu
NDA 208078
FIRDAPSE (Amifampridine Phosphate)

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Glossary

AE	Adverse event
Ach	Acetycholine
ALT	Alanine amino transferase
AST	Aspartate amino transferase
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CMAP	Compound Muscle Action Potential
CMC	Chemistry, manufacturing, and controls
CRF	Case Report Form
CRT	Clinical review template
CSR	Clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Event
ECG	Electrocardiogram
eCTD	Electronic common technical document
EMG	Electromyography
EU	European
FDA	Food and Drug Administration
GCP	good clinical practice
GGT	Gamma-glutamyl transferase
LEMS	Lambert-Eaton Myasthenic Syndrome
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	Integrated summary of effectiveness
ISS	Integrated summary of safety
ITT	Intent to treat
LV	Left ventricular
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New drug application
NME	New molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology

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OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCS	Potentially clinically significant
PK	Pharmacokinetics
PMC	Post-marketing commitment
PMR	Post-marketing requirement
PP	Per Protocol
PPI	Patient package insert
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PSUR	Periodic Safety Update report
QD	Once daily
QID	Four Times a Day
QMG	Quantitative Myasthenia Gravis
REMS	Risk evaluation and mitigation strategy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGI	Subject Global Impression
SOC	System Organ Class
SCLC	Small cell lung cancer
TEAE	Treatment emergent adverse event
T25FW	Timed-25- foot walk
3TUG	Triple Timed Up and Go
TID	Three times a day
ULN	Upper Limit of Normal
VGCC	Voltage-gated calcium channel

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1. Executive Summary

1.1. Product Introduction

Drug and Indication: FIRDAPSE® (Amifampridine phosphate) is a new molecular entity (NME) that is proposed for the (b) (4) treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults.

During the development program, the other names that are used for drug product are 3,4-diaminopyridine phosphate, 3,4-DAP phosphate, 3,4- pyridinediamine, phosphate (1:1); pyridine-3,4-diamine phosphate; and diamino-3,4-pyridine, phosphate salt. Throughout this review the product will be referred to as amifampridine phosphate or FIRDAPSE®.

Pharmacological Class: Amifampridine phosphate is a voltage-dependent potassium channel blocker. It is proposed that the blockade of potassium ion channels prolongs depolarization of the presynaptic membrane and slows down or inhibits repolarization. This prolongs calcium influx to the nerve terminal, which in turn induces exocytosis of synaptic vesicles containing acetylcholine (Ach), thus releasing an increased level of ACh into the synaptic cleft. The influx of ACh into the presynaptic cleft is thought to enhance neuromuscular transmission, providing improved muscle function.

Dosage Form: FIRDAPSE® is proposed to be marketed as oral white, round, flat-faced scored tablets. Amifampridine is the active moiety of the amifampridine phosphate tablets, and each tablet contains the equivalent of 10 mg of amifampridine.

Proposed Dosage Regimen:
The proposed starting dose is (b) (4) a day in divided doses 3-4 times a day.
The dose can be increased by 5 mg per day every 3-4 days.
The dose should not increase a maximum daily dose of 80 mg per day.
The maximum single dose is 20 mg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Based on the review of the two adequate well controlled studies with clinically meaningful endpoints, this review concludes that there is substantial evidence of effectiveness for the use of amifampridine phosphate in the treatment of LEMS in adults.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

Amifampridine phosphate (FIRDAPSE®), a new molecular entity, is proposed to be used for the treatment of Lambert- Eaton myasthenic syndrome (LEMS) in adults 18 years of age or older. LEMS is an autoimmune disease, caused by the development of antibodies against the voltage-gated calcium channel (VGCC) on nerve endings. Autoantibodies target the VGCCs of the presynaptic membrane, impairing the entry of calcium into the nerve terminal and decreasing the probability of acetylcholine (Ach) release from the synaptic vesicles. The lowered levels of acetylcholine in these patients are not sufficient to cause normal muscle contractions, causing muscle weakness. Amifampridine phosphate is a voltage-dependent potassium channel blocker that is proposed to prolong calcium influx to the nerve terminal, which in turn induces exocytosis of synaptic vesicles containing acetylcholine (Ach), thus releasing an increased level of ACh into the synaptic cleft. The influx of ACh into the presynaptic cleft is thought to enhance neuromuscular transmission, providing improved muscle function.

LEMS usually begins in later adulthood and is primarily a disease of middle aged and older people. The most common age for the appearance of symptoms is 60 years. In 50-60% of the patients with LEMS, small cell lung carcinoma (SCLC) is present when weakness begins or is found later. Death is usually from the underlying cancer in patients with SCLC-LEMS or paraneoplastic LEMS. Non-tumor LEMS (NT-LEMS) or non-paraneoplastic LEMS, is seen in all ages, with a peak of age of onset of 35 years and a larger peak at 60 years. NT-LEMS has a near normal survival rate.

Progressive proximal muscle weakness is the major clinical presentation with LEMS, and the hip girdle is generally more affected than the shoulder girdle. Patients typically develop increasing difficulty rising from a chair, lifting their feet to walk, and have a characteristic waddling gait. Respiratory failure can occur late in the course of the disease. Compared with patients who have non-paraneoplastic LEMS, patients with paraneoplastic LEMS typically have a more rapidly progressive course with a greater degree of weakness involving proximal and distal arm muscles and distal leg muscles. The prevalence of LEMS is estimated at 1/250,000 to 1/333,300 worldwide. In the United States there are approximately 950 to 1,300 individuals diagnosed with LEMS.

Currently guanidine is approved for the reduction of the symptoms of muscle weakness and easy fatigability associated with the myasthenic syndrome of Eaton-Lambert, but has serious side effects of fatal none marrow suppression, abnormal liver function and nephrotoxicity. There is

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a significant unmet clinical need for effective treatments for LEMS patients. Other treatments used include intravenous immunoglobulin, plasma exchange, immune adsorption, prednisone, azathioprine, mycophenolate.

The efficacy of FIRDAPSE® for the treatment of LEMS was demonstrated in two double-blind, placebo-controlled, randomized discontinuation studies, Studies LMS-002 and LMS-003. A total of 63 adults (age 21 to 88 years) with LEMS were enrolled in both studies. Patients taking an adequate and stable dose (30 to 80 mg per day) of amifampridine were randomized to either continue their dose of amifampridine phosphate or switched to matching placebo. The co-primary endpoints, change from baseline in Quantitative Myasthenia Gravis (QMG) and Subject Global Impression (SGI) scores, were assessed at the end of the withdrawal period on Day 14 and Day 4 for Studies LMS-002 and LMS-003, respectively. These endpoints are measures of muscle weakness and physical well-being. In both studies, patients who were randomized to placebo demonstrated a statistically significant worsening of symptoms from baseline to the end of the double-blind withdrawal period compared to patients who were maintained on amifampridine phosphate. A key secondary endpoint Clinician's Global Impression of Improvement (CGI-I) also showed statistically significant treatment benefit in favor of FIRDAPSE over placebo in both studies.

The most common adverse event occurring in the LEMS patients in the clinical studies were paresthesia (49%), upper respiratory tract infections (40%), back pain, diarrhea and muscle spasms (17%), asthenia (15%), abdominal pain, elevated liver enzymes and nausea (13%), constipation, dizziness and headache (11%). Paresthesia was more common in the treatment naïve patients (62%). Based on observations for structurally related compounds such as 4-aminopyridine, there is a potential risk of seizure with amifampridine phosphate, and seizures have been observed with amifampridine phosphate in the expanded access and registry studies.

The conclusion of this review is that substantial evidence of clinical effectiveness and an acceptable safety profile have been established to support an approval of amifampridine phosphate for the treatment of LEMS in adults.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lambert- Eaton myasthenic syndrome (LEMS) is a rare autoimmune, myasthenia-like syndrome caused by antibodies against the voltage-gated	• LEMS is a serious and disabling condition that can impact the patient's quality of life and

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	calcium channel (VGCC) on nerve endings. • The two types of LEMS are also categorized to as paraneoplastic (typically due due small cell lung cancer) and autoimmune or non-paraneoplastic LEMS. • Symptoms include progressive proximal muscle weakness, with the hip girdle generally more affected than the shoulder girdle. Patients typically develop difficulty walking, may develop difficulty swallowing, have eye movement dysfunction, and autonomic dysfunction. Many are unable to climb stairs and some become bedridden, and even require mechanical ventilation and tube feeding. • The prevalence of LEMS is estimated at 1/250,000 to 1/333,300 worldwide (www.orpha.net). In the United States, this would correspond to approximately 950 to 1,300 individuals diagnosed with LEMS.	ability to function.
Current Treatment Options	• Guanidine is approved for the reduction of the symptoms of muscle weakness and easy fatigability associated with the myasthenic syndrome of Eaton-Lambert. Guanidine has serious side effects of fatal none marrow suppression, abnormal liver function and nephrotoxicity. • Other unapproved therapies for LEMS include: intravenous immunoglobulin, plasma exchange, immune adsorption, prednisone, azathioprine, mycophenolate. • Additionally, LEMS patients are treated for the underlying cancer with antineoplastic therapies.	There is an unmet medical need for effective treatments for LEMS.
Benefit	• The efficacy of amifampridine phosphate in the symptomatic treatment of LEMS in adults was evaluated two randomized, double-blind, placebo-controlled, randomized withdrawal trials in adult patients with LEMS (Study LMS-002 and LMS-003). • Patients taking an adequate and stable dose (30 to 80 mg per day) of amifampridine were randomized to either continue their dose of amifampridine	The evidence submitted by the applicant to support the approval of amifampridine phosphate has met the statutory evidentiary standard for providing substantial evidence of effectiveness under the proposed conditions of use. The studies were adequate and well-controlled. The co-

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	phosphate or switched to matching placebo. The co-primary endpoints, change from baseline in Quantitative Myasthenia Gravis (QMG) and Subject Global Impression (SGI) scores, were assessed at the end of the withdrawal period on Day 14 and Day 4 for Studies LMS-002 and LMS-003, respectively. • Based on the primary analysis for the change from baseline in QMG and SGI score, there was a statistically significant treatment benefit for amifampridine phosphate over placebo as shown in the table below. Study | N | Co-Primary Endpoints | Treatment Difference | P-value* LMS-002 | 37 | QMG score | -1.7 (-3.4, -0.0) | 0.0452 LMS-002 | SGI score | 1.8 (0.7, 3.0) | 0.0028 LMS-003 | 26 | QMG score | -6.54 (-9.78, -3.29) | 0.0004 LMS-003 | SGI score | 2.95 (1.53, 4.38) | 0.0003 Pairwise contrast at end of double-blind from mixed-effects model repeat measures • The key secondary endpoint, Clinicians Global Impression of Improvement (CGI-I), also showed statistically significant treatment benefit in favor of amifampridine phosphate over placebo in Study LMS-002 (p=0.026) and in Study LMS-003 (p=0.002) • Differences in clinical efficacy based on age, gender, and race cannot be reliably established due to the small sample size in the two studies, although in the two studies there appeared to be no difference in treatment benefit.	primary endpoints were appropriate and clinically relevant.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The main safety data of amifampridine phosphate was generated from the two double-blind randomized withdrawal studies (LMS-002 and LMS-003) in 79 adults with LEMS. Only 63 of the adults enrolled participated in the controlled part of the two studies. The controlled safety data-base was short consisting of 7 days and 4 days respectively for the two studies. Study LMS-002 had a Run-in open phase that enrolled both amifampridine phosphate naïve and patient with prior experience with amifampridine phosphate. This study also included a 2-year open label extension. • The short duration of the controlled studies (7 days and 4 days) and randomized withdrawal design precluded the use of comparative analyses for the assessment of causality of adverse events, vital sign changes, laboratory tests, electrocardiograms. • The most common adverse event occurring in the LEMS patients that were naïve to treatment include paresthesia (62%), upper respiratory tract infections (33%), abdominal pain, diarrhea, nausea, headache, back pain, elevated liver enzymes and nausea (14%), and muscle spasms, hypertension (12%), dizziness, asthenia, muscular weakness and pain in extremity (10%) • Paresthesia was more common in the amifampridine treatment naïve patients (62%). Less frequent events of paresthesia were observed with continued use of amifampridine phosphate. • The adverse events are not dose related. • Based on observations for structurally related compounds such as 4-aminopyridine, there is a potential risk of seizure with amifampridine phosphate. Five patients reported seizures from the European LEMS Registry and the US Expanded Access program, although all cases were confounded by concomitant medication and/or prior medical history. • The risk of serious toxicity with longer term exposure and with exposure in more	The safety profile of amifampridine phosphate is acceptable to support an approval. The potential of seizures with amifampridine phosphate should be included in the Warnings and Precautions section of the labeling Because of limitations due to the small number of patients exposed and duration of exposure in the clinical trials, it is likely that adverse reactions not identified to date, or of a magnitude not observed to date, will occur in the postmarketing setting.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients is unknown. • Amifampridine phosphate will be administered based on tolerability and effect.	

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		X	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

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2. Therapeutic Context

2.1. Analysis of Condition

Lambert-Eaton myasthenic syndrome (LEMS) is a rare, autoimmune, myasthenia-like syndrome caused by antibodies against the P/Q-type voltage-gated calcium channel (VGCC) on nerve endings. Autoantibodies target the VGCCs of the presynaptic membrane, impairing the entry of calcium into the nerve terminal and decreasing the probability of acetylcholine (Ach) release from the synaptic vesicles. The lowered levels of acetylcholine in these patients are not sufficient to cause normal muscle contractions, causing muscle weakness.

LEMS is sub-classified into two main subgroups: LEMS combined with small cell lung carcinoma (SCLC) or paraneoplastic LEMS, and LEMS with no tumor (NT-LEMS) or non-paraneoplastic LEMS. NT-LEMS is also referred to as autoimmune LEMS. In 50-60% of the patients with LEMS, cancer is present when weakness begins or is found later. LEMS has also been associated with non-SCLC, lymphosarcoma, malignant thymoma, or carcinoma of the breast, stomach, colon, prostate, bladder, kidney, or gallbladder.

LEMS usually begins in later adulthood and is primarily a disease of middle-aged and older people. The most common age for the appearance of symptoms is 60 years. Younger LEMS patients typically do not develop cancer. Non-tumor LEMS (NT-LEMS), is seen in all ages, with a peak of age of onset of 35 years and a larger peak at 60 years.

Diagnosis of LEMS is based on clinical signs and symptoms, electrophysiological studies, and antibody testing. Progressive proximal muscle weakness is the major clinical presentation with LEMS, and the hip girdle is generally more affected than the shoulder girdle. Patients typically develop increasing difficulty rising from a chair, lifting their feet to walk, and have a characteristic waddling gait. Many are unable to climb stairs and some become bedridden, and even require mechanical ventilation and tube feeding. Also, facial weakness, eye muscle complaints, bulbar muscular weakness, and distal limb weakness are relatively common. Autonomic dysfunction may also be a prominent feature of LEMS manifesting most commonly with dry mouth, dry eyes, impotence, difficulty swallowing, and constipation. The rate of progression is much more pronounced in SCLC-LEMS than in NT-LEMS. Respiratory failure can occur late in the course of the disease. Compared with patients who have NT-LEMS, patients with paraneoplastic LEMS typically have a more rapidly progressive course with a greater degree of weakness involving proximal and distal arm muscles and distal leg muscles.

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The prevalence of LEMS is estimated at between 1/250,000 to 1/333,300 worldwide (www.orpha.net). In the United States, this would correspond to approximately 950 to 1,300 individuals diagnosed with LEMS.

Death is usually from the underlying cancer in paraneoplastic LEMS; however, the NT- LEMS group has a near normal survival rate.

2.2. Analysis of Current Treatment Options

There is no known cure for LEMS. Treatment is directed to optimizing function. Occasionally LEMS is cured in patients with an underlying cancer treated with antineoplastic therapies. Approved treatment is summarized in Table 1.

Table 1 Summary of Treatment for LEMS

Product (s) Name	Relevant Indication	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
Guanidine	Reduction of the symptoms of muscle weakness and easy fatigability associated with the myasthenic syndrome of Eaton-Lambert.	Oral Tablets 10-15 mg/kg in 3 or 4 divided doses	Not described in label	Fatal none marrow suppression, abnormal liver function, nephrotoxicity

Other off-label treatments or current care include:

- Pyridostigmine, a cholinesterase inhibitor that acts at the neuromuscular junction
- 3, 4 diaminopyridine and aminopyridine phosphate are used under expanded access investigational new drug (IND) applications
- Chemotherapy or other anti-tumor treatments for paraneoplastic LEMS
- Immunosuppressant/modulatory treatments that may include prednisone, azathioprine, and mycophenolate
- Intravenous immunoglobulin and/or plasma exchange

3. Regulatory Background

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3.1. U.S. Regulatory Actions and Marketing History

Amifampridine phosphate is a new molecular entity that is not marketed in the US. Catalyst has an ongoing expanded access protocol under which LEMS patients can receive FIRDAPSE® until the product is approved and available (Study EAP-001, IND 106263).

3.2. Summary of Pre-submission/Submission Regulatory Activity

The pre-submission regulatory summary chronologically listed in below in Table 2 includes only key clinical discussions in developing amifampridine phosphate regarding efficacy and safety that are applicable to this clinical review. The regulatory interactions regarding different review disciplines will be addressed in the respective reviews (i.e., chemistry, nonclinical, clinical pharmacology).

Table 2 Amifampridine Phosphate Summary of Presubmission of Regulatory Activity

Date	Summary of Regulatory Activities
11/12/2009	Orphan status granted for the treatment of LEMS
6/15/2010	Pre-IND meeting • (b) (4) • Agency indicated that studies of at least 3 months would be required. • Agency suggested that potentially a randomized withdrawal study would be appropriate. • Agency did not agree that safety data was adequate due to the poor quality.
12/14/ 2010	Submission of initial IND 106263 • 1/12/11: IND was placed on Partial Clinical hold for insufficient information to assess risks to human subjects as there was a structural alert for genotoxicity. Applicant was not allowed to enroll patients who do not have a history of neoplasm into any clinical study • 4/1/11: Removed Partial Clinical Hold
8/22/2013	Breakthrough Therapy Designation granted for the (b) (4) treatment of LEMS in adults
12/5/2013	Type B meeting

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	• Agency advised that QMG scor (b) (4) Agency recommended Subject Global Impression of Change (SGI) as a co-primary endpoint. Agency also recommended that Timed 25-Foot Walk could be a primary endpoint. • Positive findings from Study LMS-002 and the published studies would be acceptable for an NDA submission, but the protocols, Statistical Analysis Plan and source data would be required for the published studies to serve as supportive data
1/28/ 2015	Pre-NDA meeting • Pooling efficacy data from LMS-002 and published studies is not required in the ISE • Pooling of safety data for the assessment of the incidence of serious adverse events, such as seizures or cardiac arrhythmia, across all exposed patients that the applicant has knowledge of was recommended • Incidence rates for common non-serious events from pooled data were not required.
12/16/2015	NDA submitted for the (b) (4) treatment of LEMS and Congenital Myasthenic Syndromes (CMS) (b) (4)
2/12/2016	Refuse-to-File communication as: • NDA relied on inadequate published literature to support LEMS (b) (4) • Applicant did not submit raw data sets for the relative BA study (DAPSEL) that compare the BA of the salt and the free base; • Application was missing a full abuse potential assessment
4/7/ 2016	Type A meeting after Refuse-to-File • Results of Study LMS-002, while potentially supportive, lack the relevance, strength and consistency to allow the trial to serve as a single study in combination with confirmatory data from published studies. The published studies lacked source data. • Agency recommended that the applicant conduct a small randomized-withdrawal trial, or other designs appropriate for small short-term studies, with a clinically meaningful endpoint(s).

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10/25/2016	Clinical Special Protocol Assessment (SPA) Agreement for LEMS • For Study LMS-003, the proposed analysis of the co-primary endpoints (SGI and QMG) was acceptable. However, because of the small sample size and the nature of the categorical data for SGI, the Agency recommended that the applicant evaluate the assumption of normality and provide additional secondary and/or sensitivity analyses as necessary. • Stratification by baseline amifampridine dose (e.g., high-dose and low-dose) to balance for any potential exaggerated rebound effect of treatment withdrawal in subjects on higher doses of amifampridine was recommended.
5/16/17	Type A meeting • Obtained concurrence on the necessity of the drug discrimination study (CSS)
6/6/2017	Clinical SPA Agreement Modification • Minor administrative and clarifying changes to the agreed protocol • Included a detailed description of the statistical analysis plan

3.3. Foreign Regulatory Actions and Marketing History

After gaining approval in 2009, amifampridine phosphate as FIRDAPSE® has been marketed in the European Union by Biomarin.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The OSI review by Dr. Grandinetti found that the data generated by the sites that were inspected for both studies (LMS-002 and LMS-003) and that submitted by the sponsor appeared acceptable in support of the respective indication although monitoring practices were problematic for LMS-002. The violation did not appear to impact the overall safety and efficacy outcomes of LMS-002.

4.2. Product Quality

Reference ID: 4355903

The review was pending at the time of completion of this review. Please refer to the Office of Product Quality (OPQ) multidisciplinary review.

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

The review was pending at the time of completion of this review. Please refer to nonclinical review from Melissa Banks-Muckenfuss, PhD.

4.5. Clinical Pharmacology

There are no significant clinical pharmacology issues that would impact the assessment of clinical efficacy or safety.
Key considerations related to dosing include:

- Food decreases the exposure of amifampridine by about 18-20%; however, this reduction is unlikely to be clinically significant as the drug is titrated to effect and tolerance. Amifampridine phosphate can be administered without regard to food.
- A 3-5 fold increase in exposure was observed in slow NAT2 metabolizers, and a 2-3 fold increase in exposure was observed in patients with moderate and severe renal impairment.
- Studies in patients with hepatic impairment have not been conducted.
    - There are no specific dose adjustment recommendations for patients with renal impairment and acetylation status as doses are titrated based on efficacy and tolerability, even though exposures are higher in these patients. The efficacy studies enrolled patient with mild and moderate renal impairment and they were titrated to a tolerated effective dose. Patients with renal impairment are recommended to start dose titration with 15 mg per day.
    - The individualized dose titration from a 15 mg dose to a tolerated and effective dose in subjects with known slow acetylator status should account for individual differences in FIRDAPSE® metabolism.
    - Renally-impaired patients that are slow acetylators should be monitored closely with dosing.
    - Patients with hepatic impairment are recommended to start dose titration with 15 mg per day.

Please refer to Section 6 for a discussion of these issues in relation to the dosing regimen used in the clinical studies.

4.6. Devices and Companion Diagnostic Issues

Reference ID: 4355903

Not applicable

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Reference ID: 4355903

Table 3 Listing of Clinical Trials Relevant to this NDA

Type of Study	Study Population	Primary Objective of Study	Secondary/ Exploratory Objectives of Study	Study Design and Type of Control	Test Product, Dosage Regimen, and Route of Administration	Number of Subjects	Duration of Treatment
Controlled Efficacy Studies							
LMS-002 Phase 3 Efficacy	Patients with LEMS	Primary objectives: The co-primary efficacy endpoints were the change in Quantitative Myasthenia Gravis (QMG) score from double-blind baseline (Day 1, Part 2) to Day 14 (end of Part 3) and the change in Subject Global Impression (SGI) score from double-blind baseline (Day 1, Part 2) to Day 14 (end of Part 3).	Secondary objectives: The secondary efficacy endpoints were the Day 14 (end of Part 3) Clinical Global Impression-Improvement (CGI-I) scale measurements and the change in the Timed-25-foot walk (T25FW) walking speed from double-blind baseline (Part 2, Day 1) to Day 14 (end of Part 3).	Four-part, randomized, double-blind, placebo-controlled discontinuation study with open-label extension	Amifampridine Phosphate (3,4-diaminopyridine phosphate) 15-80 mg/day Oral tablet	38	Part 1: 7-≥ 91 days Part 2: 7 days Part 3: 7 days Part 4: Open-label Long-term Safety (2 years)

Reference ID: 4355703

LMS-003 Phase 3 Efficacy	Patients with LEMS	Primary objectives: To assess clinical efficacy of amifampridine phosphate compared with placebo based upon change from baseline in the co-primary endpoints of SGI and QMG scores.	Secondary objective: To assess clinical efficacy of amifampridine phosphate compared with placebo based upon change from baseline in CGI-I score. Exploratory objectives: To explore the clinical efficacy of amifampridine as measured by Triple Timed Up and Go (3TUG), patient's most bothersome symptom question, and QMG limb domains.	Randomized, double-blind placebo-controlled discontinuation study	Amifampridine Phosphate (3,4-diaminopyridine phosphate) 30-80 mg/day Oral tablet	26	4 days
Additional Safety Studies							
Safety EAP-001	Patients with LEMS	Safety from a US Expanded Access protocol	None	Open label	Amifampridine Phosphate (3,4-diaminopyridine phosphate) 20-80 mg/day Oral	143	28-1024 days
Safety EU Registry	Patients with LEMS	Safety	None	Observational and non-interventional, No controlled assessments	Amifampridine Phosphate (3,4-diaminopyridine phosphate) Oral tablet	105 in Registry 76 on Firdapase	NA

Reference ID: 4355703

Other Studies (Clinical Pharmacology: Single Dose)							
Type of Study	Study Population	Primary Objective of Study	Secondary/ Exploratory Objectives of Study	Study Design and Type of Control	Test Product, Dosage Regimen, and Route of Administration	Number of Subjects	Duration of Treatment
Phase 1 DAPSEL LMS-001 (food) FIR-001 REN-002 (Renal)	Healthy Volunteers	PK	Safety	Open label or double-blind crossover	Maximum single dose given: 30 mg/day 70 mg/kg in QTC study		Mostly Single Dose In one study 20 mg/day for Up to 4 days

Reference ID: 4355703

5.2. Review Strategy

The eCTD submission was submitted via the electronic gateway at Application 208078. I reviewed the two pivotal clinical efficacy studies (LMS-002 and LMS-003) along with Dr. Junshan Qui, Ph.D. Dr. Qui provided summaries of the Statistical Analysis Plan and the efficacy analyses results for incorporation in this review.

I reviewed the clinical safety of this application with guidance on safety review strategy from Dr. Gerard Boehm, MD.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. LMS-002

6.1.1. Study Design

Overview and Objective

The primary objective of Study LMS-002 was to compare the efficacy of amifampridine phosphate versus placebo on muscle strength in subjects with LEMS at the end of a 14-day Withdrawal and Treatment period as evaluated by the Quantitative Myasthenia Gravis (QMG) score and the Subject Global Impression (SGI) score.

Trial Design

Study initiation: 12 Sep 2011
Study Completion: 29 Jul 2014 (Parts 1-3)

The study is a Phase 3, multicenter, double-blind, placebo-controlled, randomized withdrawal study in adult patients diagnosed with LEMS. Placebo was the control during the randomized withdrawal/discontinuation phase. The study consisted of 4 parts, with Parts 1, 2, and 3 completed in the clinic and Part 4 completed as an outpatient open-label extension as shown in Figure 1.

Part 1: Open-label run-in
This part was designed to allow patients to achieve an optimal dose and a minimum duration of amifampridine phosphate exposure before the randomized withdrawal/discontinuation phase. The optimal dose regimen was defined as the dose regimen that resulted in a ≥3-point improvement in the QMG score from Screening for patients who were not receiving

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amifampridine treatment at the time of entry into the Run-in Period. Improvement in the QMG score was not required for patients already taking amifampridine at the time of entry into the Run-in Period.

The requirements for Part 1 were as follows: (1) optimal neuromuscular benefit; (2) at least 91 consecutive days of amifampridine treatment (base or phosphate); (3) at least 7 consecutive days of a stable amifampridine phosphate dose (i.e., the same total daily dose and dose regimen) immediately before entering Part 2; and (4) stable regimen of best supportive care consisting of a duration of 91 consecutive days of immunotherapy or 7 consecutive days of cholinesterase inhibitor, where applicable.

Part 2: Double-blind treatment discontinuation/withdrawal

Patients were randomized using IXRS in a double-blind fashion in a 1:1 ratio to either (1) continued treatment with amifampridine phosphate for 7 days or (2) discontinued treatment with amifampridine phosphate via a downward titration to placebo over 7 days. Rescue treatment was provided to patients who experienced treatment failure. Unless the clinical condition of the patient was severe enough to dictate otherwise, patients who met rescue treatment criteria were discontinued from Part 2 and proceeded to Rescue Visit 1 for safety and efficacy evaluation. After 8 to 24 hours of Rescue Visit 1, patients proceeded to a confirmatory Rescue Visit 2, at which time rescue treatment (e.g., amifampridine phosphate) could be provided.

Treatment failure was defined as becoming non-ambulatory, having an increase (worsening) in QMG score by greater than 5 points, or developing respiratory failure requiring mechanical ventilation.

Part 3: Double-blind treatment

Patients remained on Part 2-assigned amifampridine phosphate or placebo for an additional 7 days for a total of 14 days in the randomized, blinded and placebo-controlled portion of the study. Efficacy and safety assessments were performed on Day 8 and Day 14 following the standardized schedule. Urine samples collected on Days 8 and 14 were assayed for 3-N-acetyl amifampridine metabolite to verify compliance with the prohibition against the use of other sources of amifampridine during the double-blind treatment period. Those requiring a rescue treatment during Part 3 of the study proceeded directly to Rescue Visit 2. Those deemed eligible to receive amifampridine phosphate treatment by the investigator were provided the option to receive open-label amifampridine phosphate and proceeded to Part 4, Open-label Long-term Safety. Those who were not eligible proceeded to the early termination visit.

Part 4: Open-label extension

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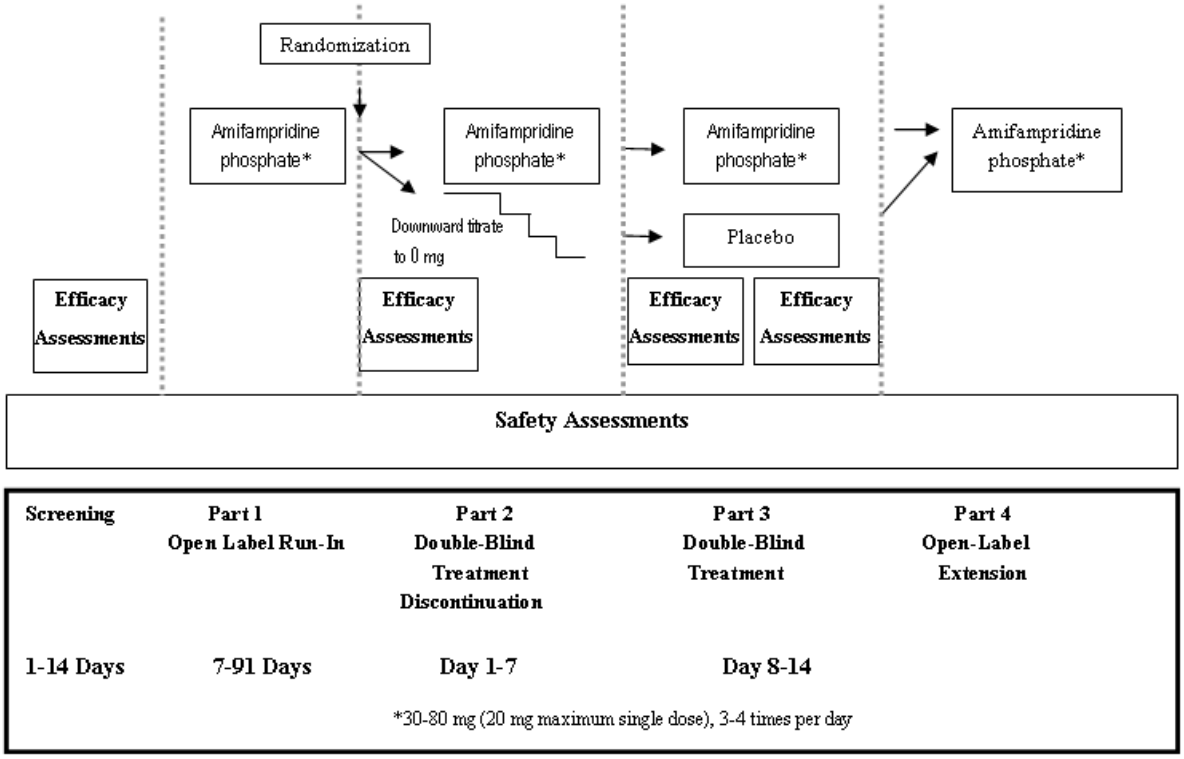
Patients who completed Parts 1, 2, and 3 were eligible to participate in an open-label extension for up to 2 years of amifampridine phosphate treatment (LMS-002EXT). Also, patients requiring rescue during either Part 2 or Part 3 were eligible to enroll directly into Part 4 and resume amifampridine phosphate treatment.

Figure 1 LMS-002 Study Design



Source: LMS-002 Protocol, NDA 208078

Dose: In Part 1 (Open-label Run-in), the dose of amifampridine phosphate was individually determined by the investigator, within the bounds of a 15 mg to 80 mg total daily dose, given in 3 to 4 divided doses, with a maximum of 20 mg at any single oral administration. All doses were taken with food.

- In patients already taking amifampridine base, amifampridine phosphate was started at an equivalent or lower equivalent dose of amifampridine base, at the investigator's discretion.
- Treatment-naïve patients were allowed to start at a dose as low as 15 mg per day (5 mg, 3 times daily) with upwards titration. Before entry into Part 2 of the study, all patients were escalated to a 30 mg to 80 mg total daily dose, with a maximum of 20 mg at any single administration.

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For upward titration, amifampridine phosphate was to be increased by 10 mg increments every 4 to 5 days to a maximum of 80 mg per day, based on optimal neuromuscular benefit and at the discretion of the investigator.
Urine samples were collected during Part 2 and Part 3 on Days 1, 8, and 14 for analysis of levels of the major metabolite of amifampridine, 3-N-acetyl amifampridine, to verify compliance.

Reviewer Comment:
The dosing regimen was supported by numerous published controlled and uncontrolled studies and case reports. Amifampridine phosphate has a short half-life of 1.8 hours; therefore, it will require 3-4 times daily administration. A few considerations regarding dosing are discussed below:
Effect of food on dosing: *Food decreases the exposure of amifampridine by about 18-20%. This reduction is unlikely to be clinically significant as the drug is titrated to effect and tolerance. In addition, given the TID or QID administration of amifampridine phosphate, administering drug without food will not be practical.*
Effect on renal impairment on dosing: *A 2-3 fold increase in exposure was observed in patients with moderate and severe renal impairment. In this study there were 2 patients with CrCL of 54 and 49 mL/min, indicating moderate renal impairment. These patients were titrated up to 40-50 mg/day in this study. Patients with severe renal impairment were excluded from the study, providing no experience on dosing these patients. However, since the doses are individually titrated to tolerability and effect, further dose adjustment in the renal impairment are of less concern.*
Effect on acetylation status on dosing: *A 3-5 fold increase in exposure was observed in slow NAT2 metabolizers. In this study the slow metabolizers received doses of 30-80 mg/day. In addition, 70% of the patients were slow metabolizers and 24% were intermediate metabolizers and 6% were fast acetylators; hence, the study overall provides experience on such patients. There were 3 fast acetylators enrolled in the study; one received 80 mg/day during the study and two others were randomized to placebo. Therefore, experience on optimal dosing for the fast acetylators is minimal. However, since the doses are individually titrated to tolerability and effect, additional dosing recommendations related to acetylator status is less of a concern. There is no experience on dosing slow acetylators that are renally impaired. Such patients will also be titrated to effect. It is noteworthy that the slow acetylators have higher exposure than the patients with severe renal impairment, providing assurance that there is experience in dosing patients with higher exposure in this study and their tolerability/safety assessments.*

Blinding: The applicant has made efforts to keep the blinding intact. The placebo tablets were indistinguishable from amifampridine phosphate tablets. To maintain the blind during Part 2, subjects were provided with daily dose packets containing a constant number of tablets. Also, the same individual rater did not perform both the compound muscle action potential (CMAP)

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and QMG tests on an individual patient. QMG was the primary and CMAP a tertiary endpoint in the study.

Study location: The study was conducted at 13 sites in 8 countries, including France, Germany, Hungary, Poland, Russia, Serbia, Spain, and the United States.

Key Inclusion Criteria:

- ≥18 years of age, with confirmed diagnosis of LEMS with acquired (typical) proximal muscle weakness and at least 1 of the following:
  - – Nerve conduction findings (CMAP that increased at least two-fold after maximum voluntary contraction of the tested muscle)
  - – Positive anti-P/Q type voltage-gated calcium channel antibody test
- A QMG score of ≥5 for individuals without any prior symptomatic treatment for LEMS
- A forced vital capacity of ≥80% of predicted value if subject had no history of other current respiratory disease and was receiving amifampridine for LEMS, or forced vital capacity ≥60% of predicted (defined as normal) if not receiving amifampridine for LEMS at study inclusion.
- Normal swallowing function as defined by the ability to swallow 4 ounces of water without coughing or throat clearing (score of 0 on this dimension of QMG)
- Completion of anticancer treatment at least 3 months (90 days) before screening
- If receiving peripherally acting cholinesterase inhibitors (e.g., pyridostigmine), a stable dose of cholinesterase inhibitors was required for at least 7 days prior to Screening.
- If receiving permitted oral immunosuppressants (e.g., prednisone or other corticosteroid, azathioprine, mycophenolate), a stable dose was required for at least 90 days prior to Screening.
- If sexually active, willing to use 2 acceptable methods of contraception from Screening until 3 months after the last dose

Key Exclusion Criteria:

- History of epilepsy or seizure
- Concurrent use of dalfampridine (4-aminopyridine), and any form of 3,4-diaminopyridine in the study
- Forced vital capacity <1500 mL at screening
- Use of intravenous immunoglobulin G (IVIG), plasmapheresis (plasma exchange), within 90 days, guanidine hydrochloride within 7 days, or rituximab within 12 months prior to screening
- Use of medications that lower seizure threshold or inhibit neuromuscular junction function prior to Screening

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- Patients with history of cardiac problems or risk factors, severe renal (creatinine clearance <30 mL/min), hepatic problems (AST and ALT >ULN in non-cancer patients and >5XULN in cancer patients, uncontrolled asthma (specifics included in the protocol)

Study Endpoints

Primary: The efficacy was assessed with two co-primary endpoints:

- Change in QMG score from double-blind baseline (Day 1, Part 2) to Day 14 (end of Part 3)
  The QMG is a physician rated test including 13 assessments including facial strength, swallowing, grip strength, duration of time that limbs can be maintained in outstretched positions, and forced vital capacity. Each item of the scale is graded with scores of 0-3 denoting none, mild, moderate and severe impairment respectively with higher scores indicating greater disability. The total score of QMG is 39.
- Change in SGI score from double-blind baseline (Day 1, Part 2) to Day 14 (end of Part 3). The patients were asked to rate their impression of the effects of the study drug during the preceding week on their physical well-being.
  The SGI is a 7-point scale on which the patients rated their global impression of the effects of the study treatment (1 = Terrible; 2 = Mostly Dissatisfied; 3 = Mixed; 4 = Partially Satisfied; 5 = Mostly Satisfied; 6 = Pleased; 7 = Delighted).

Reviewer's Comment:
The endpoints for the study were discussed with applicant in the Type B meeting in December 2013. The Agency recommended that these co-primary endpoints (change in QMG and SGI) could be acceptable. (b) (4) *A co-primary endpoint of SGI was recommended to assess the clinical meaningfulness of changes on the QMG.*

Secondary:

- The Clinical Global Impression-Improvement (CGI-I) scale measurement on Day 14 (end of Part 3).
  The 7-point scale was scored by the investigator (1 = Very much improved; 2 = Much improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; 7 = Very Much Worse)
- The change in the T25FW walking speed (feet/minute) from double-blind baseline (Part 2, Day 1) to Day 14 (end of Part 3)

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The T25FW test is a quantitative mobility and leg function performance test based on a timed 25-foot walk. Following a rest of at least 5 minutes, the timed 25-foot walk was repeated. The test was the average speed expressed in feet/minute.

Tertiary:

- Compound Muscle Action Potential (CMAP) amplitude
  CMAP amplitude is an objective laboratory measure. CMAP amplitude at rest decreases proportionally with the severity of neuromuscular block and the severity of LEMS
- Clinical Global Impression-Severity (CGI-S)
  The CGI-S is a 7-point scale that was used to assess the investigator's global impression of symptom severity at a given point in time.

Exploratory:

- Plasma levels of amifampridine and its major metabolite, 3-N-acetyl amifampridine
- Relationship between NAT genetic polymorphism status and plasma levels of amifampridine and 3-N-acetyl amifampridine

Statistical Analysis Plan (Reviewed by Dr. Junshan Qiu)

The following information was extracted from the Integrated Summary of Efficacy (ISE) included in the submission, and the clinical study report (CSR).
The statistical analysis plan (SAP) finalized for study LMS-002 was Version 2.0 (12-JUNE-2017).

Version 0 June 12, 2014
Version 1 September 05, 2014
When the reporting database was validated and locked for analysis was not provided.

General Statistical Issues Applied to Study LMS-002

The following general statistical issues were defined or specified in the SAP.

Patient Populations for Analysis
All randomized subjects who received at least one dose of investigational product (amifampridine phosphate or placebo) in Study Part 2 and who had at least one post-baseline efficacy assessment. Subjects were analyzed as randomized.

Specification of Baseline
For each variable, baseline was either defined as the last non-missing value prior to the receiving the first dose of amifampridine phosphate (Part 1, Day 1 – applicable to laboratory, vital sign and ECG data only) or last non-missing value prior to the first dose of double-blind study medication (Part 2, Day 1).

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Handling of Missing Data

Subjects who had Part 3 rescue assessments had these assigned to the next scheduled assessment for analysis purposes. For example, a subject who had a rescue assessment without having scheduled post-baseline data had their rescue assessment assigned as a Day 8 assessment. Subjects with a rescue assessment subsequent to a scheduled day 8 assessments had their rescue assessment assigned as a Day 14 assessment for analysis purposes.

Primary Efficacy Analyses

A mixed effect model repeated measures (MMRM) model was used to analyze each component of the co-primary endpoint. The dependent variable was the change from double-blind baseline (Day 1, Part 2) to the Day 8 and Day 14 Part 3 assessments. The model included treatment, time (Day 8, Day 14), treatment-by-time interaction and double-blind baseline score (baseline QMG for the QMG endpoint and baseline SGI for the SGI endpoint) as fixed effects and subject as a random effect. The models assumed time effect was random between subjects. The p-values corresponding to the treatment comparisons were determined using a permutation test. The p-value was calculated as the proportion of records for which a randomized replicate had smaller p-value than the p-value of the original dataset. Both the QMG and the SGI treatment comparisons need to be significant using a two-sided test at the alpha=0.05 level of significance using the permutation test.

Multiplicity

A step-down method was used. The first secondary outcome measure (CGI-I) would only be formally statistically tested if the two co-primary endpoints are statistically significant, and the second secondary outcome (T25FW) would be formally statistically tested if and only if the primary endpoints and the first secondary outcome measure are all statistically significant. Thus, no adjustment for multiplicity was needed.

Sample Size Determination

Following a review of Sanders et al., a total of 36 subjects need to be randomized to provide 80% power to detect a difference of 2.44 units in the mean change of the QMG scores between the 2 treatment groups, assuming a type I error of 0.05 and a common standard deviation of 2.5.

Protocol Amendments

The original protocol for study LMS-002 was approved on December 08, 2010; there were 5 protocol amendments (amendment 1 on January 12, 2011, amendment 2 on April 19, 2011, amendment 3 on September 14, 2011, amendment 4 on Dec 22, 2011 and amendment 5 on February 8, 2013).

Sensitivity Analyses:

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- The coefficients in the model were estimated by generalized least squares (GLS), with parameters estimated by restricted maximum likelihood (REML).
- An analysis of covariance (ANCOVA) model, based on observed data at Day 14 only, was fitted.
- The ANCOVA model above was repeated except last observation carried forward (LOCF) was used.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that the study was conducted in accordance with the US Code of Federal Regulations (21 CFR Parts 50, 56, and 312) and other national and local regulations, as applicable, and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP).

Financial Disclosure

The applicant provided certification that there was no financial agreement with the clinical investigators defined in 21 CFR Part 54.2. Financial disclosure and certification information was submitted in module 1.3.4 included in Form FDA 3454 with Certification from applicant for those investigators (Box 1 checked) with no disclosable financial interests or arrangements. The applicant appended a list of clinical investigators to Form FDA 3454.

Patient Disposition

Screening/enrollment: Screened*: 74 patients, Enrolled: 54 patients; Reason of Withdrawal of 20 patients: not all eligibility criteria met.
[*Note: 3 more patients were screened but had no data in the database; therefore, a total 77 were screened]

Part 1: 54 entered Part 1; withdrew: 14 patients (5 dues to AEs, 3 due to personal reasons, 2 due to lack of efficacy, 1 due to physician decision and 3 due to other reasons), transferred to Part 4: 2 patients as enrollment target was met.
Part 2: 38 patients were randomized, completed: 37 patients, Rescued: 1 patient
Part 3: Completed 36 patients: Rescued: 1 patient prior to completion of Part 3
Part 4: Total 40 patients in open label extension. 36 patients from Part 3, 2 patients directly from Part 1, 2 patients from Part 2
Patients Analyzed: 53 patients were included in the safety analysis population (Patient (b) (6) was enrolled, but did not have any data after Screening). The full analysis set included all patients who received at least 1 dose of study drug (amifampridine phosphate or placebo) in

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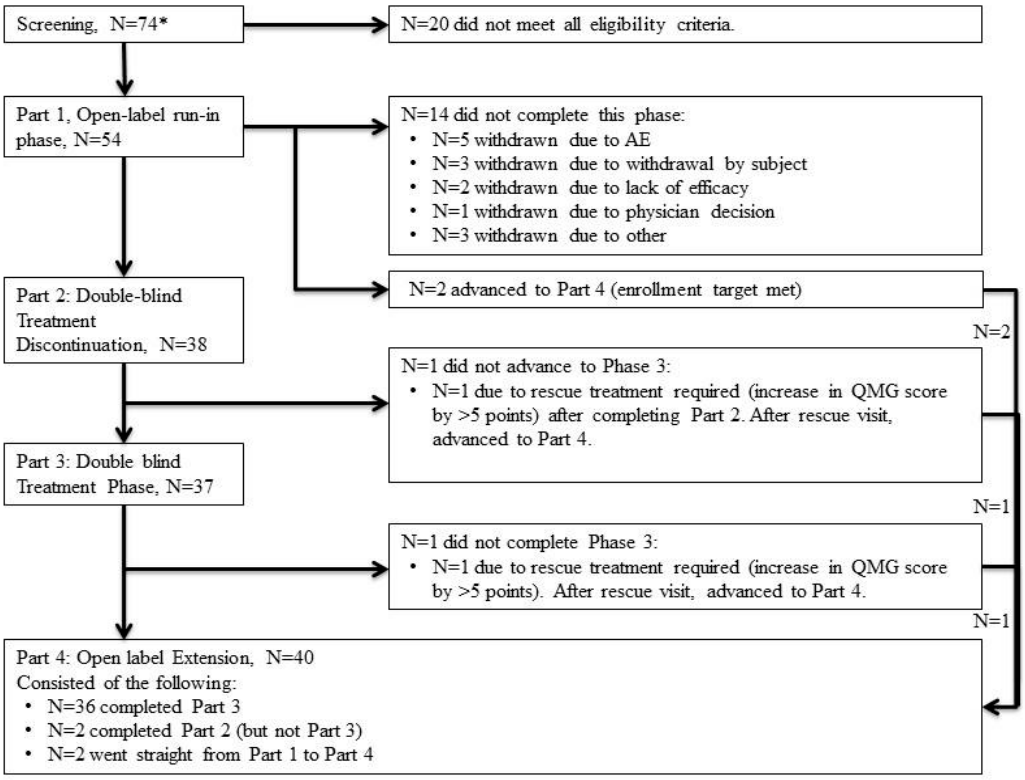
Part 2 and who had at least 1 post baseline efficacy assessment. The patient who was rescued in Part 2 did not have a post baseline efficacy assessment and so was not included in the full analysis set. Therefore, the primary analysis included 37 patients, 22 on placebo and 16 on amifampridine phosphate.

Figure 2 Disposition of Patients in Study LMS-002



Note: The randomization scheme was stratified to equalize treatment groups for treatment-naïve and treatment-experienced patients; however, this stratification was performed after the first 9 patients had already been randomized (when the study was taken over by Catalyst from BioMarin). This led to an overall imbalance in the number of patients assigned to each treatment (i.e., 22 patients were assigned to the placebo group, and 16 patients were assigned to the amifampridine group). Overall stratification also led to more patients being treatment-naïve.

Reviewer's Comment:

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Two patients were rescued during the study. Patient (b) (6) rescued during part 2 of the study and patient (b) (6) rescued during Part 3 of the study on Day 8. The primary analysis included all patients who received at least 1 dose of study drug (amifampridine phosphate or placebo) in Part 2 and who had at least 1 post baseline efficacy assessment. The sensitivity analyses with the exclusion of these patients are described in the results section of the review.

Protocol Violations/Deviations

Table 4 lists major protocol deviations that could impact the efficacy analysis as it relates to dosing and assessments. Notably, 10 major protocol deviations occurred at one site (number 2007) in Moscow, Russia, primarily pertaining to dosing error (not being dosed prior to Day 14 assessments). These are not included in Table 4.

Table 4 Major Protocol Deviations

Patient	Details	Probable Impact on Efficacy Assessments
(b) (6)	Patient was not dosed with blinded medication prior to Day 14 assessments (a major protocol violation given its potential impact on the efficacy outcomes).	Under dosed (on drug)
(b) (6)	Patient was administered 3 tablets in error during the first dosing of the day during Parts 2 and 3. Per the Medical Monitor's instructions, the patient was administered 1 tablet during the middle of the day and 2 tablets in the evening.	Dose error (on placebo)
(b) (6)	On Day 1 through 14 (Parts 2 and 3), patient took only 4 tablets per blister per day instead of all of the tablets per day.	Under dosed (on drug)
(b) (6)	On Day 2 (Part 2), this patient took tablets from the incorrect blister kit.	Dose error (on drug)
(b) (6)	On Day 1 (Part 2), patient took twice the assigned dose.	Under dosed (on drug)
(b) (6)	Remained on bid dosing	Under dosed (on placebo)
(b) (6)	Received a suboptimal dose of study drug during Part 2 (30 mg not 60 mg per protocol)	Under dosed (on drug)
(b) (6)	During Part 1, patient was started on a total daily dose of 10 mg amifampridine at the discretion of the investigator.	No impact

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(b) (6)	On Day 1 (Part 2), patient took twice the assigned dose.	Maybe efficacy and safety both (on drug)

Source: Adapted from CSR LMS-002
Note: The table excludes the 10 patients from Russia that had dosing error. In addition, the other protocol deviations could impact safety and will be taken into account in the Safety review in Section 7 of the review as necessary.
*This violation was discovered after database lock

Reviewer's Comment:
I looked into the probable impact of these major deviations on efficacy assessments, as shown in the third column in Table 4*. The review of individual data shows that the major deviations are not likely to bias the results in favor of amifampridine, as many under dosed subjects were on amifampridine phosphate and should have experienced a reduction in efficacy. Many of these errors occurred in the early part of Part 2 or 3.*

In addition, for all 10 patients at the Russian site, the last dose of medication occurred about 12-16 hour prior to the efficacy measurements instead of within the allotted window of time. These patients would have experienced reduction in efficacy, which would bias the results against amifampridine. The sponsor has conducted a post-hoc analysis excluding this site. Despite this, statistical significance was achieved for the co-primary endpoints, even with fewer number of patients (38 vs. 27).

Demographics and Baseline Characteristics

Demographics and Baseline characteristics for all 53 patients enrolled who received at least 1 dose of amifampridine phosphate and had any post-treatment safety information collected (Safety Population) and all 38 patients who were randomized to the double-blind period is summarized in Table 5.

Table 5 Demographic Characteristics

	Part 1 Patients*	**Part 2 and 3 Patients****		
Parameter	**N = 53**	**Placebo N = 22**	**Amifampridine N = 16**	**Overall N = 38**
Age at Screening (years)				
Mean ± SD	52 ± 16	52 ± 18	52 ± 12	52 ± 15
Median (min, max)	55 (20, 88)	57 (21, 88)	53 (25, 67)	54 (21, 88)
Sex, n (%)				
Male	18 (34%)	8 (36%)	7 (44%)	15 (40%)
Female	35 (66%)	14 (64%)	9 (56%)	23 (61%)

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If female, is the patient of child-bearing potential?				
Yes, n (%)	10 (29%)	5 (36%)	3 (33%)	8 (35%)
No, n (%)	25 (71%)	9 (64%)	6 (67%)	15 (65%)
Ethnicity, n (%)				
Hispanic or Latino	4 (8%)	0	3 (19%)	3 (8%)
Not Hispanic or Latino	48 (91%)	22 (100%)	12 (75%)	34 (90%)
Not Reported	1 (2%)	0	1 (6%)	1 (2%)
Race, n (%)				
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Black or African American	1 (2%)	0	0	0
Native Hawaiian/Pacific Islander	0	0	0	0
White	48 (9%)	21 (95 %)	13 (81%)	34 (90%)
Other	2 (4%)	0	2 (13%)	2 (5%)
Not Reported	2 (4%)	1 (5%)	1 (6%)	2 (5%)
Was the patient taking amifampridine (base or phosphate) immediately prior to enrollment?				
Yes, n (%)	11 (21%)	7 (32%)	3 (19%)	10 (26%)
No, n (%)	42 (79 %)	15 (68%)	13 (81%)	28 (74%)
If yes, number of continuous days of amifampridine exposure immediately prior to enrollment				
Mean ± SD	1410 ± 1909.	1287 ± 1526	2143 ± 3080	1544 ± 1957
Median (min, max)	402 (70, 5700)	630 (166, 4457)	365 (365, 5700)	516 (166, 5700)

*54 enrolled, but 53 received at least 1 dose of amifampridine and had any post treatment safety data
**The full analysis set included all 38 patients who received at least 1 dose (amifampridine or placebo) in Part 2 and who had at least 1 post baseline efficacy assessment.
Abbreviations: max = maximum; min = minimum; N = number of patients; n = number of patients in the sample; SD = standard deviation

Reviewer's Comment:
Overall, the study population consisted of twice as many females compared to males. The numbers of males in the placebo versus amifampridine phosphate treatment groups were comparable, although fewer in the study. Autoimmune LEMS has equal prevalence in men and women, however, the ratio of men: women is 13:4 in patients with paraneoplastic LEMS. With respect to race, about 90% of the population was of the population was White. The mean/median number of continuous days of amifampridine exposure immediately prior to enrollment varied between treatment groups, although the number of subjects on amifampridine at enrollment was much smaller (7 and 3 in treatment and placebo arms) to show any impact of difference in exposure prior to enrollment within groups. The number of

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patients naïve to amifampridine was greater in the treatment arm compared to placebo, which could impact the tolerability of the drug. Overall, there were no significant differences in demographic characteristics that could bias the efficacy results in favor of amifampridine phosphate.

Number of subjects at each starting dose in the Run-In phase and the Double-Blind Phase is shown in Table 6. This shows that 27 patients in this study started the titration phase in this study at doses <30 mg/day [redacted] (b) (4), as the protocol allowed the treatment naïve patients to start at a lower dose. In the double-blind phase 8/16 patients in the amifampridine phosphate group were titrated up to 80 mg/day (maximum recommended dose). This shows adequate exposure to the proposed doses in this study.

Table 6 Number of subjects at each starting dose in the Run-In Phase and the Double-Blind Phase

Run-In Phase (N=53)		Double-blind Phase in Part 3 (N=37)	
Starting Dose (mg/day)	Number of Subjects	Dose in the double-blind Phase at randomization (mg/day)	Number of subjects
10	3	0	21
15	20	30	1
20	4	40	3
30	17	50	1
40	4	60	2
50	1	70	1
60	4	80	8
80	1		

Other Baseline Characteristics

As summarized in Table 7, of the 38 patients who entered the double-blind phase, 32 (84%) of autoimmune LEMS diagnosis and 6 (16%) were paraneoplastic. More than 80% had autoimmune LEMS in both placebo and amifampridine treatment groups. The mean duration of LEMS was longer in the amifampridine group (6.5 years) compared to the placebo group (3.4 years).

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Table 7 Other Baseline Disease Characteristics

	Part 1 Patients	Part 2 and 3 Patients		
Parameter	**N = 53**	**Placebo N = 22**	**Amifampridine N = 16**	**Overall N = 38**
Current LEMS Diagnosis n (%)				
Paraneoplastic	9 (17%)	3 (14%)	3 (19%)	6 (16%)
Autoimmune	44 (83%)	19 (86%)	13 (81%)	32 (84%)
Duration of LEMS (years)				
Mean ± SD	4 ± 5	3± 4	7 ± 8	5 ± 6
Median (min, max)	2 (0.1-22)	2 (0.1-14)	2 (0.7-21.5)	2 (0.1-22)
QMG at Part 2, Day 1[a] Mean ± SD (Lower score favorable)	6 ± 4	6 ± 4	6 ± 3	6 ± 4
SGI score at Part 2, Day 1 (n)				
Score 1	0	0	0	0
Score 2	0	0	0	0
Score 3	1	0	1	1
Score 4	6	4	2	6
Score 5	9	5	4	9
Score 6	7	3	4	7
Score 7	15	10	5	15
(Higher score favorable)				
CGI-S Score				
Score 1	NA	0	1	1
Score 2		4	0	4
Score 3		11	4	15
Score 4		5	10	15
Score 5		1	1	1
Score 6		1	0	1
Score 7		0	0	0
(Lower Scores favorable)				
Timed 25-foot walk test at Day 1 (Feet/min)	248 ± 122	244 ± 121	254 ± 126	248 ± 122

Abbreviations: max = maximum; min = minimum; N = number of patients; n = number of patients in the sample; SD = standard deviation

[a] sum of scores for QMG arms and legs were comparable between treatments

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About 50-60% of the LMS population is paraneoplastic. This study enrolls more patients with a diagnosis of autoimmune LEMS. It is unlikely that the symptomatic effect of amifampridine phosphate would differ between patients with paraneoplastic and autoimmune LEMS. The duration of LEMS was longer in the amifampridine phosphate arm compared to the placebo arm, but this should not impact the results due to the symptomatic effect of amifampridine phosphate.

Overall for both QMG and CGI, the placebo group has scores that suggest patients are less impaired, which would not favor the amifampridine phosphate group to show a treatment effect, hence, this will not affect the interpretability of the study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Urine was collected to assess treatment compliance. All used and unused drug containers were to be returned. There were no concerns on compliance.

I reviewed the concomitant medications and supportive care in the amifampridine phosphate and placebo arms in the Run-in phase of the study for the patients that were randomized in Part 2 of the study. There were a few more patients in the placebo group that were on other supportive care medications than in the amifampridine phosphate group as shown in Table 8 . The concomitant medication use during the study would not confound the interpretation of the study results in favor of amifampridine phosphate as more patients were on supportive care in the patients randomized to placebo.

Table 8 Number of Patients with Concomitant Supportive Care Medications

Concomitant Drug	Amifampridine Phosphate	Placebo
Anticholinesterases	10	14
Calcium	0	1
Calcium, combinations with vitamin D and/or other drugs	0	1
Diaminopyrimidines	1	1
Glucocorticoids	8	11
Immunoglobulins	1	0
Other immunosuppressants	2	2
Potassium	0	2
Vitamin D and analogues	0	1

Note: same patient could be on multiple supportive care medications

Reviewer's Comment:

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Diaminopyrimidine was prohibited during the study. One patient in each treatment arm was on diaminopyrimidine, hence concomitant use of this will not bias the study results.

Two subjects were rescued during the double-blind phase of the study due to the increase in QMG score of >5 points. One patient was rescued during Part 2 of the study and another during Part 3 of the study. Their inclusion in the analysis was per the protocol. The rescued patients were transferred to Part 4 (open-label) of the study.

Efficacy Results – Co-Primary Endpoint

The co-primary efficacy endpoints were:

- The change in QMG score from double-blind baseline (Day 1, Part 2) to Day 14 (end of Part 3) and
- The change in SGI score from baseline (Day 1, Part 2) to Day 14 (end of Part 3).

A MMRM model was used to analyze each component of the co-primary endpoint while a permutation test was selected to provide the corresponding p-value. The results reported by the applicant in the analyses of the co-primary endpoints were confirmed by Statistical Reviewer Dr. Junshan Qiu as shown in Table 9.

There was statistically significant mean between-group difference favoring amifampridine group compared to placebo in change from baseline (Day 1, Part 2) to Day 14 in both QMG or SGI scores. The LS mean change from baseline in QMG scores during the double-blind treatment phase was 0.4 for amifampridine compared with 2.2 for placebo. The LS mean change from baseline in SGI scores during the double-blind treatment phase was -0.8 for amifampridine compared with -2.6 for placebo.

Table 9 shows that both the change in QMG and SGI scores from baseline to Day 14 reached statistical significance in favor of amifampridine (p=0.0452 and 0.0028, respectively).

Table 9 Change in Co-primary endpoints QMG and SGI scores from Baseline (Day 1, Part 2) to Day 14 (End of Part 3): Full Analysis Dataset

Assessment	Amifampridine phosphate	Placebo
	N = 16	N = 21
Quantitative Myasthenia Gravis Scores		
Baseline (Mean ± SD)	6.4 ± 3.22	5.6 ± 3.99
Day 14 (Mean ± SD)	6.7 ± 4.09	7.9 ± 2.85

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Change from Baseline (Mean ± SD)	0.3 ± 2.60	2.2 ± 2.93
LS mean change from baseline	0.4	2.2
Difference in LS means (amifampridine phosphate minus placebo (95% CI)	–1.7 (–3.4, –0.0)	
p-value (MMRM)	0.0452*	
p-value (Permutation Test)	0.046	
Subject Global Impression Scores		
Baseline (Mean ± SD)	5.6 ± 1.26	5.9 ± 1.22
Day 14 (Mean ± SD)	4.9 ± 1.57	3.2 ± 1.70
Change from Baseline (Mean ± SD)	-0.7 ± 1.82	-2.7 ± 2.29
LS mean change from baseline	–0.8	–2.6
Difference in LS means (amifampridine phosphate minus placebo (95% CI)	1.8 (0.7, 3.0)	
p-value (MMRM)	0.0028*	
p-value (Permutation Test)	0.003	

Source: NDA208078 \\cdsesub1\evsprod\nda208078\0001\
*Pairwise contrast at Day 14 from MMRM model including subject (b) (6) sensitivity analyses without this patient is shown in Table 10.
Note: Lower scores in QMG are favorable and Higher scores in SGI are favorable)

The number of patients with magnitude of change on QMG and SGI score is shown in histogram in Figure 3 and Figure 4. These figures demonstrate that more placebo subjects (orange bars) perform worse on Day 14 on both QMG and SGI scores. The patients performing worse on treatment are from the Russian site (2007), where a dosing error occurred when the dose was administered 14 hours before the assessment.

Figure 3 Magnitude of Individual Change in Total QMG score on Day 14

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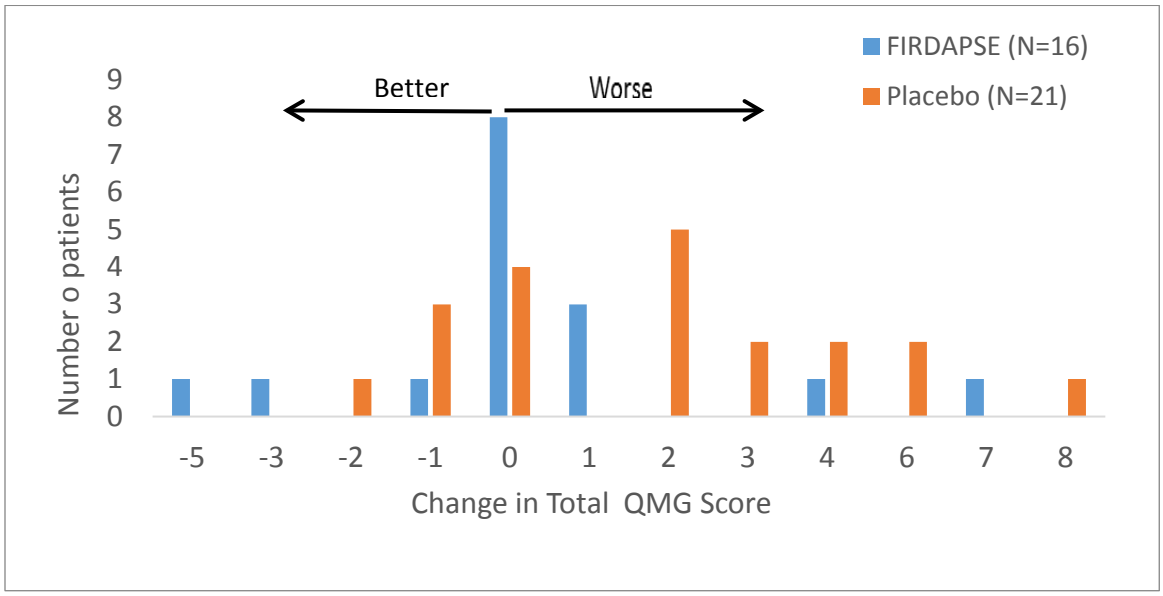
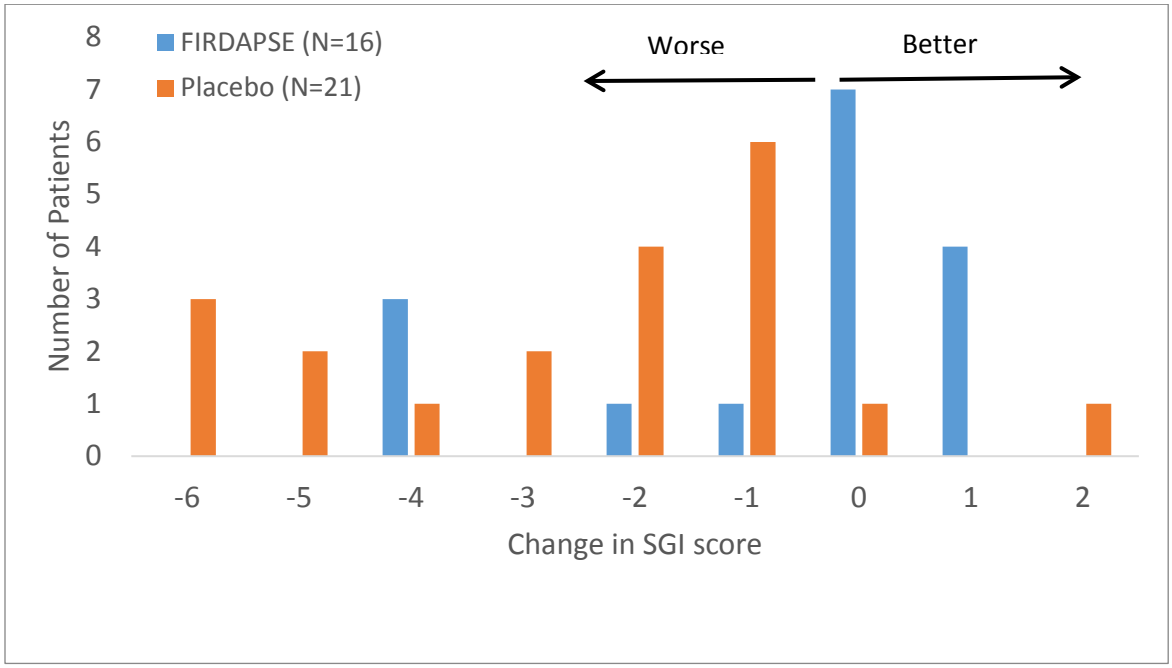


Figure 4 Magnitude of Individual Change in SGI score on Day 14



Additional Co-primary Efficacy Analyses

Sensitivity analyses:

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A few sensitivity analyses were performed on the co-primary endpoints by the applicant and confirmed by Dr. Junshan Qiu as shown in Table 10.

The treatment group comparison using the ANCOVA model on QMG at Day 14 using observed data failed to achieve statistical significance (p=0.084) with a treatment group difference of -1.4. The treatment group comparison using the ANCOVA model on SGI at Day 14 using observed data was statistically significant (p=0.007) with a treatment group difference of 1.6.

The treatment group comparison using the ANCOVA model on QMG and SGI at Day 14 using last observation carried forward (LOCF) was statistically significant in favor of amifampridine phosphate (p=0.032 and 0.003, respectively).

Table 10 Sensitivity analyses on co-primary endpoints QMG and SGI

Model	QMG	SGI
	p-value	
ANCOVA (observed)*	0.084	0.007
ANCOVA (LOCF)**	0.032	0.003

*Two rescued patients were excluded from the analysis
**Two rescued patients were included in the analysis

Data Quality and Integrity

There were data quality issues with the protocol deviations and OSI findings but these didn't effect the interpretability of the study results.

Efficacy Results – Secondary and other relevant endpoints

The results from the MMRM on the CGI-I Scores at Day 14 (end of Part 3) showed statistically significant mean treatment difference of -1.1 in favor of amifampridine phosphate (p=0.0267) with LS mean score of 3.6 for amifampridine phosphate and 4.7 for placebo. However, the results from the MMRM on the change in T25FW walking speed from Baseline (Day 1, Part 2) to Day 14 (end of Part 3) revealed no statistically significant treatment group differences (p=0.6274) as shown in Table 11. These results were confirmed by Dr. Junshan Qui.

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Table 11 Change in Secondary endpoints CGI and T25FW from Baseline (Day 1, Part 2) to Day 14 (End of Part 3): Full Analysis Dataset

Assessment	Amifampridine phosphate	Placebo
	N = 16	N = 21
Clinical Global Impression-Improvement Scores		
Baseline (Mean ± SD)	2.6 ± 0.63	2.5 ± 0.98
Day 14 (Mean ± SD)	3.6 ± 1.50	4.8 ± 1.45
LS mean change from baseline	3.6	4.7
Difference in LS means (amifampridine phosphate minus placebo (95% CI)	–1.1 (–2.1, –0.1)	
p-value (MMRM)	0.0267*	
p-value (Permutation Test)	0.02	
Timed 25-Foot Walk (feet/minute)		
Baseline (Mean ± SD)	254 ± 126	255 ± 111
Day 14 (Mean ± SD)	253 ± 126	245 ± 116
Change from Baseline (Mean ± SD)	-1.46 ± 52.5	10.4 ± 53.1
LS mean change from baseline	–1.16	–9.67
Difference in LS means (amifampridine phosphate minus placebo (95% CI)	8.51 (–26.77, 43.79)	
p-value (MMRM)	0.6274*	
p-value (Permutation Test)	0.6346	

Source: NDA208078 \\cdsesub1\evsprod\nda208078\0001\
**Pairwise contrast at Day 14 from MMRM model
Note: CGI: Lower Scores are favorable

Reviewer's Comment:
The variability was high in the assessment of the T25FW, therefore, the study power could be low to detect a treatment difference.

Tertiary and Exploratory Endpoint

The applicant evaluated several tertiary and exploratory endpoints. These are only considered exploratory as these analyses were not controlled for Type 1 error. The endpoint that were in favor of amifampridine include: Change from double blind baseline in Day 8 in QMG score (nominal p=<0.0001), Change on QMG subscore for the arms subdomain both at Day 8 (nominal p=<0.0001) and Day 14 (p=0.048), Change in T25FW walking speed from baseline to Day 8 (p=0.030), Change in CMAP amplitude on Day 8 (p=0.006), CGI-I scores on Day 8 (p=0.017), Change in SGI scores from baseline to Day 8 (p=0.001).

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The endpoints that did not favor amifampridine phosphate include: Change on QMG subscore for the legs subdomain both at Day 8 and 14, Change in CMAP amplitude on Day 14, percentage change in CMAP amplitude between first and fifth CMAP in the first series of 3Hz stimuli at Days 8 and 14, change in CGI-S score from baseline to Day 8 and 14.

Reviewer's Comment:
Most of the tertiary endpoints are alternative analyses of the primary and secondary endpoints, QMG, SGI, CGI and T25FW. The exploratory endpoint, change on QMG subscore for the legs subdomain both at Day 8 (p=0.15) and 14 (p=0.055) was not nominally positive. In addition, the change in Timed 25-Foot Walk, though nominally positive on Day 8 (p=0.03), was not nominally significant on Day 14 (p=0.63). In LEMS, the hip girdle is generally more affected than the shoulder girdle. Patients typically develop increasing difficulty rising from a chair, lifting their feet to walk, and have a characteristic waddling gait. Hence, one would expect improved effect on lower extremity function. The CMAP results are very weak as well. The results of the co-primary analyses on QMG and SGI are not corroborated with the other measures of lower extremity function. This weakens the results of the co-primary analysis.

Dose/Dose Response

Dose-response relationship was not evaluated in this study. Doses between 30-80 mg/day were given based on individual response in the open label 91-day run-in phase.

Additional Analyses Conducted on the Individual Trial

Post Hoc Analyses Excluding Russian Site

There were 11 subjects in the Russian site that were not dosed on Day 14 (Part 3 of the Study) prior to the analysis of the primary endpoint. A post-hoc analysis was performed by the applicant excluding the subjects at the Russian site 2007. The study was positive regardless of this major protocol violation.
A MMRM analysis was performed by the applicant on the co-primary endpoint the change in QMG and SGI scores from Baseline (Day 1, Part 2) to Day 14 (end of Part 3) excluding data from the Russian site (number 2007). As shown in Table 12, the treatment difference for change from baseline in QMG and SGI scores was statistically significant in favor of amifampridine (p=0.0060 and 0.0010, respectively).

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Table 12 Co-primary endpoints QMG and SGI excluding Russian Site 2007

	Amifampridine phosphate	Placebo
	N = 10	N = 16
Quantitative Myasthenia Gravis Scores		
Baseline (Mean ± SD)	6.5 ± 3.34	5.9 ± 4.12
LS mean change from baseline*	-0.6	2.2
Difference in LS means (amifampridine phosphate minus placebo (95% CI)	–2.8 (–4.7, –0.9)	
p-value[a]	0.0048	
Subject Global Impression Scores		
Baseline (Mean ± SD)	4.9 ± 0.99	5.6 ± 1.26
LS mean change from baseline	–0.3	–2.4
Difference in LS means (amifampridine phosphate minus placebo (95% CI)	2.1 (0.9, 3.4)	
p-value	0.0019	

Source: NDA208078 \\cdsesub1\evsprod\nda208078\0001\
*Estimated via a MMRM with the scores at Day 8 and Day 14 as the dependent variable and terms for treatment, time (Day 8, Day 14), treatment-by-time interaction, and double-blind baseline QMG score as fixed effects and patient as a random effect. The model assumed time effect to be random between patients.

Conclusions

Statistically significant treatment differences in favor of amifampridine phosphate compared to placebo were observed in the co-primary endpoints, the change in QMG (p=0.046) and SGI scores (p=0.003) during the 14-day double-blind discontinuation and treatment phase of the study.

Statistically significant mean difference in favor of amifampridine phosphate compared to placebo was also observed for the secondary endpoint CGI-I score (p=0.02) on Day 14. For the secondary endpoints, a step-down method was used. The first secondary outcome measure (CGI-I) would only be formally statistically tested if the two co-primary endpoints are statistically significant, and the second secondary outcome (T25FW) would be formally statistically tested if and only if the primary endpoints and the first secondary outcome measure are all statistically significant. Thus, no adjustment for multiplicity was needed. No statistically significant treatment difference in favor of amifampridine phosphate was observed for change from baseline T25FW (p=0.634).

The tertiary and exploratory endpoints that were mostly alternative analyses of the primary and key secondary endpoints provided weak evidence of effectiveness based on nominal p-

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values. The only unique exploratory endpoint was CMAP. Only one of the 6 CMAP analyses were nominally positive (Change in CMAP amplitude on Day 8, p=0.006). CMAP was not nominally positive on Day 14 (the time of co-primary analyses) (p=0.639). Other desirable endpoints that measured lower extremity function, such as QMG Leg Domain and T25FW were not nominally positive.

Overall, the positive results on the co-primary endpoints of Study LMS-002 are supportive of the overall efficacy of amifampridine phosphate in LEMS, but the results are not robust across the secondary endpoints and the sensitivity analyses. The applicant's post-hoc analyses removing the Russian site that had dosing error lowered the p-value in the smaller subset of patients, indicating that the data integrity issues identified with this site do not appear to impact the overall positive findings of the study.

6.2. LMS-003

6.2.1. Study Design

Overview and Objective

The primary objectives of the study were to assess the clinical efficacy of amifampridine phosphate compared to placebo in patients with LEMS, based upon improvement in the subject global impression (SGI) and QMG score.

Trial Design

Study initiation: 13 Jan 2017
Study Completion: 30 Oct 2017

This was a randomized withdrawal, double-blind, placebo-controlled, parallel-group study in patients diagnosed with LEMS. Prior to randomization into the study, patients were receiving unblinded treatment in the expanded access program (EAP-001). Patients had to be on a stable dose and frequency of amifampridine phosphate for at least 1 week prior to randomization. Patients who met eligibility criteria were randomized 1:1 to amifampridine phosphate (at the patient's optimal dose) or placebo on Day 0. The randomization was stratified by low dose (<60mg/day) and high dose (≥60mg/day) of amifampridine phosphate.

Baseline assessments were obtained on Study Day 0. Patients took blinded study medication on Day 1 through Day 3. On Day 4, a dose of blinded study medication was administered by the site study personnel. This was the same medication that the patient took on Day 1 through Day 3. The assessments were performed following either the second, third, or fourth dose of medication taken on Day 4, and this was the same dose after which Day 0 assessments were

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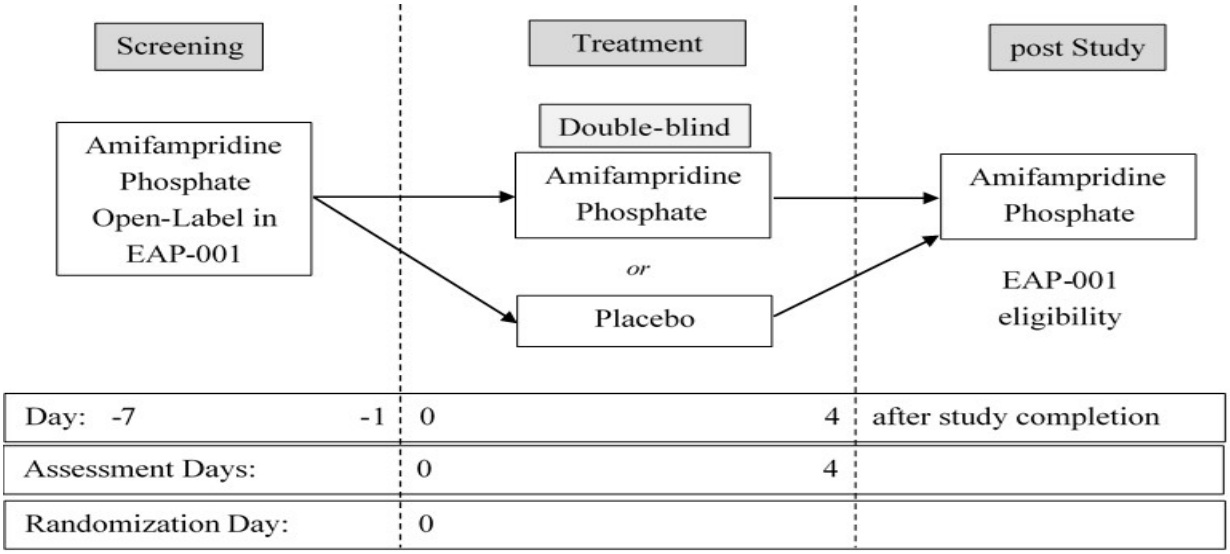
performed. For example, if the patient took their second dose of amifampridine phosphate in the clinic on Day 0 and had assessments 40 minutes later, then on Day 4, that patient was assessed after taking their second dose of amifampridine phosphate. The planned duration of participation for each patient was up to 12 days, including screening (up to 7 days), Day 0 assessments and treatment administration (Day 1 through Day 4). A total of 26 subjects were enrolled into this study. A schematic of the study design is shown in Figure 5.

Figure 5 LMS-003 Study Design



Dose:
The amifampridine phosphate dose was 30 mg to 80 mg total daily dose, given in 3 to 4 divided doses as prescribed by the Investigator, based on optimal neuromuscular benefit and tolerability. No single dose was >20 mg. Doses of study treatment were taken outside the clinic, except during the in-clinic study visits on Day 0 and Day 4. Doses were taken <u>without regards to meals</u>.

Reviewer's Comment:
The doses in this study were taken without regard to meals, unlike Study LMS-002, where doses were taken with meals. The decrease in exposure with food is 18-20%. Given that doses are titrated to effect and tolerance, the administration of drug with regard to food is unlikely to cause meaningful loss in efficacy.

Blinding:

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The blinding of the study appears adequate. The unblinded personnel dispensing the identical active drug and placebo tablets were not involved in any observation, monitoring, or reporting required by the study protocol.

Study location:
The study was conducted at 3 sites in the US.

Key Inclusion Criteria:

- Male or female ≥18 years of age with LEMS and who were receiving a stable dose of amifampridine phosphate for at least 7 days
- Diagnosis of LEMS by antibody testing or nerve conduction studies
- Completion of anti-cancer treatment at least 3 months prior to Screening
- A stable dose for at least 7 days if receiving pyridostigmine or at least 30 days if on immunosuppressants (prednisone or other corticosteroid) prior to randomization and throughout the study

Key Exclusion Criteria:

- Clinically significant long QTc interval on ECG in previous 12 months
- Seizure disorder
- Active brain metastases
- Unable to ambulate
- Patients who could not discontinue immunomodulatory treatment (e.g., mycophenolate, azathioprine, cyclosporine) within 3 weeks before screening

Reviewer's Comment:
A difference between the exclusion criteria of study LMS-003 and LMS-002 was that Study LMS-003 did not exclude patients on current use of dalfampridine or any other form of 3,4, DAP at any time and the use if guanidine hydrochloride within 7 days of screening, where Study LMS-002 did. The inclusion criteria required subjects to be on a stable dose of amifampridine phosphate for at least 7 days. I looked into the number of subjects in each treatment arm that were on these drugs as they could impact the efficacy evaluations. All patients were on stable doses of amifampridine phosphate. There were no subjects on guanidine in the study. Therefore, the impact of prior use of any of these drugs would not confound the evaluation of symptomatic effect of amifampridine phosphate.
Study LMS-002 excluded patients on oral immunosuppressants with the exception of glucocorticoids while Study LMS-003 did not. It is unlikely that they would affect the results.

Study Endpoints

Primary: The efficacy was assessed with two <u>co-primary</u> endpoints:

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- Change in QMG score from baseline (Day 0) to post treatment (Day 4)
- Change in SGI score from baseline (Day 0) to post treatment (Day 4)

These are the same endpoints as study LMS-002.

Secondary:

- The Clinical Global Impression-Improvement (CGI-I) scale measurement on Day 4.

Exploratory:

- Triple Timed Up and Go (3TUG): The 3TUG is a functional mobility test that requires a patient 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 3 times without pause, and the measurement is the average time required to complete each of the 3 repetitions.
- Patient's most bothersome symptom: 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.
- QMG limbs

Statistical Analysis Plan (reviewed by Dr. Junshan Qiu)

The following information was extracted from the ISE and CSR. The statistical analysis plan (SAP) finalized for study LMS-003 was Version 1.0 (12-JULY-2017). When the reporting database was validated and locked for analysis was not provided.

General Statistical Issues Applied to Study LMS-003

The following general statistical issues were defined or specified in the SAP.

Patient Populations for Analysis

The population consists of all randomized subjects who receive at least 1 dose of investigational product (IP) (amifampridine phosphate or placebo) and have at least one post-treatment efficacy assessment.

Specification of Baseline and Post-treatment

Baseline was evaluated at Day 0. The post-treatment result was obtained on Day 4, unless the subject discontinued treatment early, in which case the post-treatment result might be obtained at an earlier time point.

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Handling of Missing Data

No missing data imputation was used in this analysis. All analyses were based on observed data. For subjects that discontinue prior to Day 4 due to treatment related disability ("Rescue"), the observations collected at the time of rescue was to be analyzed with the other Day 4 observations.

Primary Efficacy Analyses

The co-primary endpoint of change from baseline for total QMG score was analyzed using analysis of covariance (ANCOVA) with QMG at baseline as the only covariate.
The co-primary endpoint of change from baseline for total SGI score was analyzed using analysis of covariance (ANCOVA) with SGI at baseline as the only covariate.

Sample Size Determination

For Change from Baseline in QMG Scores, a between-treatment difference of -2.8 and a standard deviation at most 3.07, as observed in LSM-002, a sample size of at least 11 patients per sequence would provide power of 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 patients per sequence would 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 patients, equally randomized to two treatment sequences, would provide power of at least 80% for each of the two co-primary endpoints.

Sensitivity Analyses:

A sensitivity analysis of the co-primary endpoints was conducted to evaluate the patterns of early treatment discontinuation.

Secondary endpoints

CGI-I: A Wilcoxon Rank Sum Test was conducted to assess for treatment group differences in CGI-I

Exploratory endpoints

3TUG: The number and proportion of patients with at least a 20% increase in average time for 3TUG (i.e,, a success) at Day 4 relative to Day 0 was tested using Fisher's Exact Test.
Patient Most Bothersome Symptom (PMBS) Question: The analysis of change from baseline for the PMBS score was performed using Wilcoxon's Rank Sum Test.
QMG Limb Domains: A fixed-effects linear model with terms of treatment and baseline were used to assess treatment differences.

Protocol Amendments

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The original protocol for study LMS-003 was approved on September 02, 2016; there were 2 protocol amendments (amendment 1 on September 18, 2016 and amendment 2 on April 27, 2017). This study had an SPA agreement.

Protocol amendment 1 modified the study design from 2 treatment periods for a total of 8 days to a single dosing period for total participation duration of 5 days.

Protocol amendment 2 included the following changes: clarified inclusion criteria #1 and #5; added exclusion criteria #4, #5, and #7; clarified that screening and randomization could occur on the same day; clarified the timeframes for prohibited medications, clarified the planned efficacy analyses.

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that the study was conducted in accordance with the US Code of Federal Regulations (21 CFR Parts 50, 56, and 312) and other national and local regulations, as applicable, and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP).

Financial Disclosure

The applicant provided certification that there was no financial agreement with the clinical investigators defined in 21 CFR part 54.2. Financial disclosure and certification information was submitted in module 1.3.4 included in Form FDA 3454 with Certification from applicant for those investigators (Box 1 checked) with no disclosable financial interests or arrangements. The applicant appended a list of clinical investigators to Form FDA 3454.

Patient Disposition

All enrolled subjects, stratified to low and high dose groups completed the study as summarized in Table 13.

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Table 13 Summary of Patient Disposition

Disposition	Amifampridine N=13		Placebo N=13	
	Low Dose (<60mg/day)	High Dose (≥60mg/day)	Low Dose (<60mg/day)	High Dose (≥60mg/day)
Enrolled, n (%)	4 (30.8)	9 (69.2)	5 (38.5)	8 (61.5)
Completed study, n (%)	4 (30.8)	9 (69.2)	5 (38.5)	8 (61.5)
Withdrawn, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Reviewer's Comment:
A total of 9 out of the 26 patients enrolled had also participated in Study LMS-002, but the conduct of the two study were several years apart.

Protocol Violations/Deviations

The applicant reported a few minor protocol deviations. None of reported protocol deviations would affect the efficacy analyses.

Reviewer's Comment: One patient was on immunoglobulin in the amifampridine phosphate arm, which was prohibited in this study. The impact of this was negligible as discussed under concomitant medications section of this review.

Demographics and Baseline Characteristics

Baseline demographics are presented in Table 14. Patients in the low dose amifampridine phosphate and placebo groups were younger and weighed less than those in the high dose groups.

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Table 14 Summary of Demographic Data and Baseline Characteristics

	Amifampridine N=13			Placebo N=13			Overall N=26		
	All	Low Dose	High Dose	All	Low Dose	High Dose	All	Low Dose	High Dose
Age (years), mean (SD) Median Range	55 (12) 59 33-71	53 (14) 57.5 33-66	56 (11) 60 42-71	53 (13) 52 31-75	50 (13) 52 31-64	55 (14) 50.5 40-75	54 (12) 55.5 31-75	np	np
Weight (kg), mean (SD)	78 (20)	72 (11)	80 (24)	94 (15)	90 (13)	96 (17)	86 (20)	np	np
Gender, n (%)									
Male	6 (46)	2 (15)	4 (31)	4 (30)	0 (0.0)	4 (31)	10 (39)	2 (8)	8 (31)
Female	7 (54)	2 (15)	5 (40)	9 (70)	5 (39)	4 (31)	16 (61)	7 (27)	9 (35)
Ethnicity, n (%)									
Hispanic or Latino	4 (31)	2 (15)	2 (15)	1 (8)	0 (0.0)	1 (8)	5 (19)	2 (8)	3 (12)
Not Hispanic	9 (69)	2 (15)	7 (54)	12 (92)	5 (39)	7 (54)	21 (81)	7 (27)	14 (54)
Race									
White	10	4	6	13	8	5	23	9	14
Asian	1	0	1	0	0	0	1	0	1
Black	1	0	1	0	0	0	1	0	1
Other	1	0	1	0	0	0	1	0	1

Source LMS-003 CSR
Low dose is <60mg/day. High dose is ≥60mg/day.
Abbreviations: max = maximum; min = minimum; N = number of patients; SD = standard deviation; np= not provided

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Urine was collected to assess treatment compliance. All used and unused drug containers were to be returned. If the patient was taking pyridostigmine, the dosing schedule was fixed in relation to when they took amifampridine, such that on the days of clinic assessments the timing between pyridostigmine dose and amifampridine did not vary. There was no significant difference in the use of any supportive care, such as pyridostigmine or corticosteroids between the treatment arms as shown in Table 15.

Prohibited Medications

The following medications were prohibited before and during the study:

- immunomodulatory treatment (e.g., azathioprine, mycophenolate, cyclosporine) within 3 weeks before Screening
- intravenous immunoglobulin G within 2 weeks before Screening

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- plasmapheresis (plasma exchange or therapeutic plasma exchange) 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

Table 15 Number of Patients with Concomitant Supportive Care Medications

Concomitant Drug	Amifampridine Phosphate	Placebo
Anticholinesterases	8	7
Glucocorticoids	3	3
Immunoglobulins	1	0

Reviewer's Comment:
There was one patient on 25 gm intravenous immunoglobulin G during the study in the amifampridine phosphate arm. This was a prohibited medication during the study. However, this did not impact the efficacy results for this study, based on a sensitivity analysis conducted by Dr. Qiu excluding this patient.

Efficacy Results – Co-Primary Endpoint

The co-primary efficacy endpoints were:

- The change in QMG score from double-blind baseline (Day 0) to Day 4 and
- The change in SGI score from baseline (Day 0) to Day 4

The post-treatment result was the result obtained on Day 4, unless the patient discontinued treatment early, in which case the post-treatment result may have been obtained at an earlier time point.

Efficacy analyses followed the methods specified in the SAP. The results reported by the sponsor for the analyses of the co-primary endpoints were confirmed by Dr. Junshan Qiu. There was statistically significant mean between-group difference favoring amifampridine phosphate group compared to placebo in change from baseline (Day 0) to Day 4 in both QMG and SGI scores. For QMG total score, there was a statistically significant (p=0.0004) mean difference of -6.54 in favor of amifampridine phosphate. For SGI, there was a statistically significant (p=0.0003) mean difference of 2.95 in favor of amifampridine phosphate as summarized in Table 16.

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Table 16 Change in Co-primary Endpoints QMG and SGI Scores from Baseline (Day 0) to Day4: Full Analysis set

	Amifampridine phosphate	Placebo
	N = 13	N=13
Quantitative Myasthenia Gravis Scores		
Baseline (Mean ± SD)	7.8 ± 4.20	8.5 ± 5.43
Day 4 (Mean ± SD)	7.9 ± 4.94	15.0 ± 5.90
Change from Baseline (Mean ± SD)	0.1 ± 3.07	6.5 ± 4.82
LS mean change from baseline	0.00	6.54
Difference in LS means (amifampridine phosphate minus placebo (95% CI)	-6.54 (–9.78, –3.29)	
p-value (ANCOVA)	0.0004	
Subject Global Impression Scores		
Baseline (Mean ± SD)	6.1 ± 0.86	5.8 ± 0.90
Day 4 (Mean ± SD)	5.3 ± 1.65	2.4 ± 1.76
Change from Baseline (Mean ± SD)	-0.8 ± 1.74	-3.5 ± 2.18
LS mean change from baseline	-0.64	–3.9
Difference in LS means (amifampridine phosphate minus placebo (95% CI)	2.95 (1.53, 4.38)	
p-value (ANCOVA)	0.0003	

Source: NDA208078 \\cdsesub1\evsprod\nda208078\0007
(Note: Lower scores in QMG are favorable and Higher scores in SGI are favorable)

The individual magnitude of change in the Total QMG score and SGI score on Day 4 is shown in Figure 8. These figures show that the more number of patients on placebo performed worse on both QMG and SGI scores.

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Figure 6 Individual Magnitude of Change in Total QMG Score on Day 4

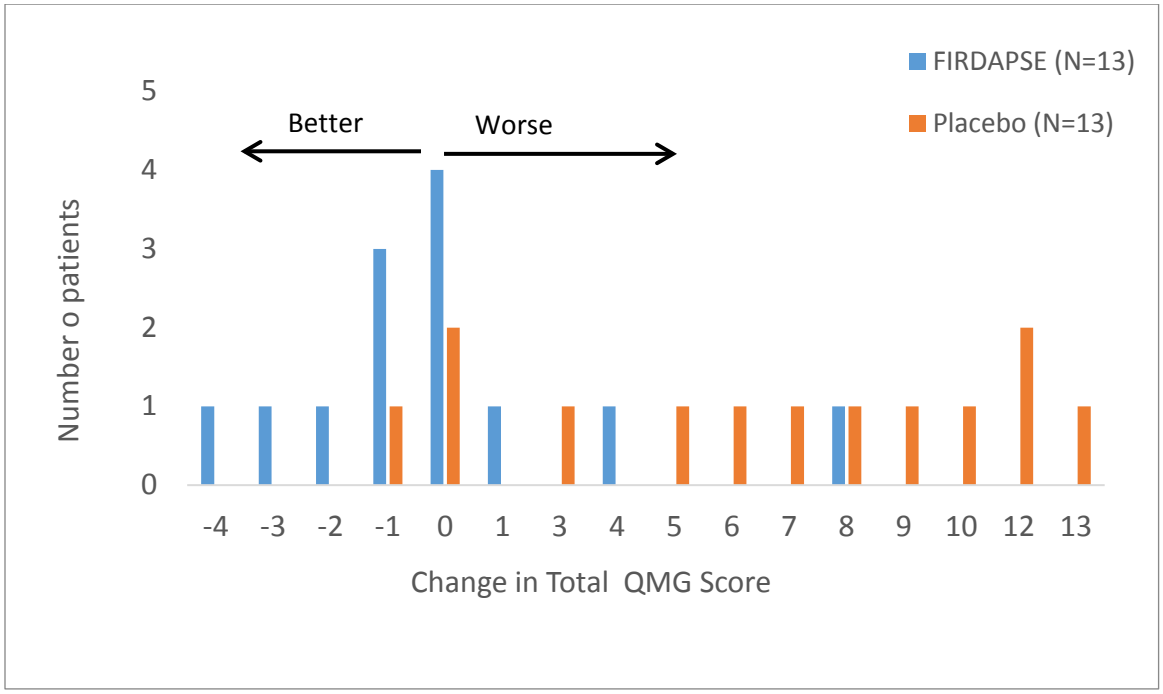
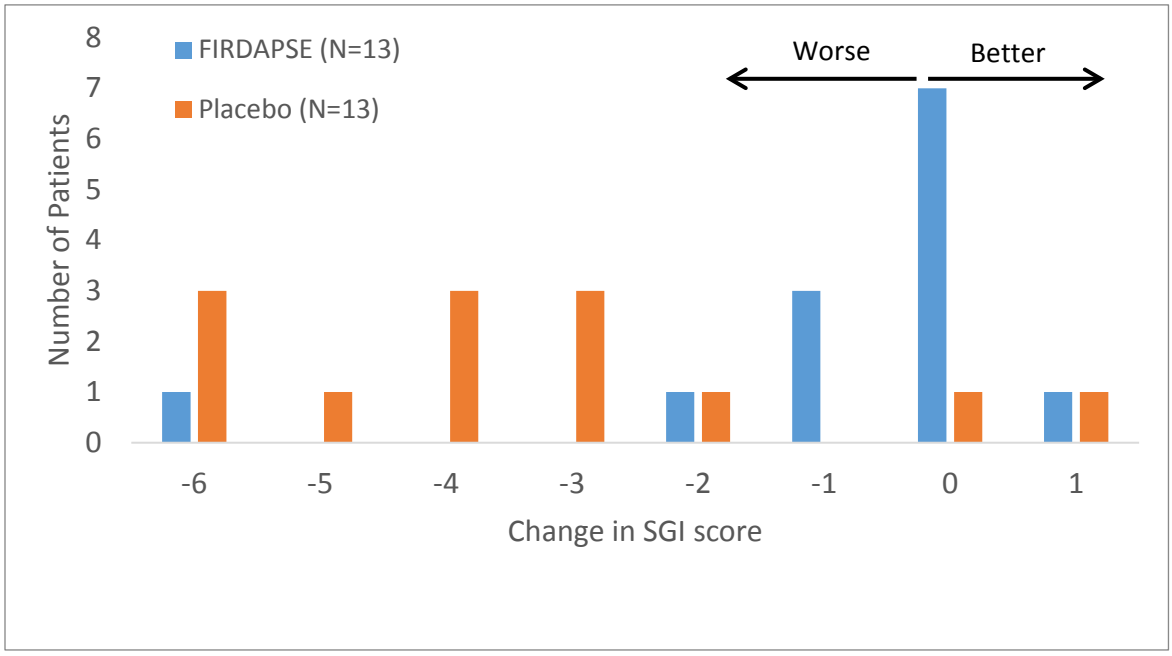


Figure 7 Individual Magnitude of Change in SGI Score on Day 4



Reviewer's Comment:

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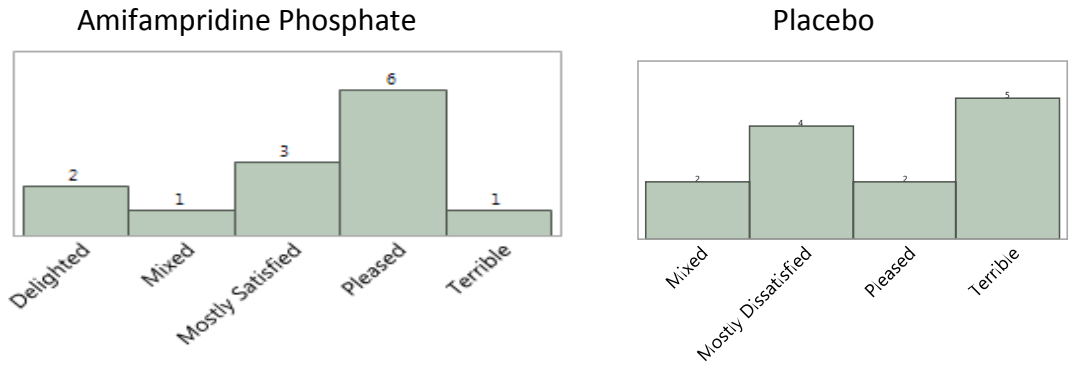
There was one patient in the >60 mg/day amifampridine phosphate dose group that felt much worse on both QMG and SGI assessments on Day 4.

The distribution of absolute SGI scoring for the amifampridine phosphate and the placebo arm on Day 4 is shown in the Figure 8.

Figure 8 Distribution of SGI scores on Day 4



Reviewer's comments: Most patients in the placebo group were dissatisfied with the improvement and most were satisfied with the improvement observed in the amifampridine phosphate arm as would be expected in a withdrawal design if the drug were to give symptomatic benefit. In this study since patients were already in the expanded access program prior to enrollment in the study, incident paresthesia was not observed. Hence, the likelihood of a patient assessment to be biased due to unblinding effects of paresthesia appear minimal.

Sensitivity Co-primary Efficacy Analyses

Sensitivity analyses were confirmed by the reviewer and these analyses corroborated the results of the primary analyses for the co-primary endpoints as shown in Table 17.

Table 17 Sensitivity analyses on co-primary endpoints

Model	QMG	SGI
	p-value	
Fixed effects linear model analysis on permuted treatment assignments*	0.0004	0.0006

Fixed effects terms for treatment and score at Baseline was added to the analysis

Summary statistics for both QMG and SGI were calculated based on the stratification factor of the dose (low and high dose) as shown in Table 18:

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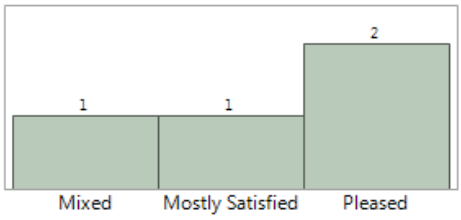
Table 18 Summary of QMG Total Scores and SGI by dose

	Amifampridine N=13		Placebo N=13	
	Low Dose (<60mg/day) N=4	High Dose (≥60mg/day) N=9	Low Dose (<60mg/day) N=5	High Dose (≥60mg/day) N=8
Quantitative Myasthenia Gravis Scores				
Day 0 (Baseline)	8.0 (4.08)	7.8 (4.49)	10.0 (7.84)	7.6 (3.58)
Post-Baseline (Day 4)	8.8 (5.68)	7.6 (4.90)	16.0 (6.96)	14.4 (5.55)
Change from baseline	0.8 (2.36)	-0.2 (3.42)	6.0 (6.28)	6.8 (4.13)
Subject Global Impression Scores				
Day 0 (Baseline)	5.5 (0.58)	6.3 (0.87)	6.2 (0.84)	5.6 (0.92)
Post-Baseline (Day 4)	5.0 (1.41)	5.4 (1.81)	2.4 (2.07)	2.4 (1.69)
Change from baseline	-0.5 (1.29)	-0.9 (1.96)	-3.8 (2.28)	-3.3 (2.25)

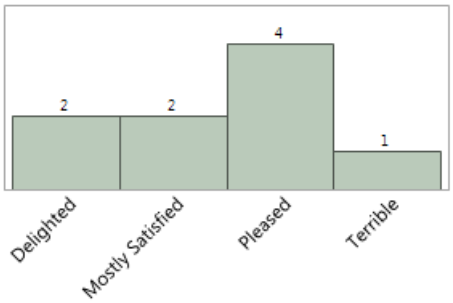
The distribution SGI scoring in patients on amifampridine phosphate arm in the low and high dose groups is shown in Figure 9

Figure 9 Distribution of SGI scores on Day 4 in Low and High Dose Groups of Amifampridine Phosphate

Low Dose (<60mg/day)



High Dose (>60 mg/day)



Reviewer's Comment: Although a trend was observed with higher doses performing better, given the small number of patients in the study such conclusions cannot be made reliably. Moreover, fewer subjects remained on lower doses.

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Data Quality and Integrity

There were no issues with data quality and integrity.

Efficacy Results – Secondary and other relevant endpoints

Amifampridine phosphate treatment resulted in a treatment difference for CGI-I that was significantly (p=0.0020) lower than that observed in the placebo group as shown in Table 19

Table 19 Change from baseline in secondary endpoint

	Amifampridine phosphate	**Placebo**
	N = 13	N=13
Clinical Global Impression-Improvement Scores		
Baseline (Mean ± SD)	NA	NA
Mean (SD)	3.8 (0.80)	5.5 (1.27)
p-value[a]	0.0020	

* Source: NDA208078 \\cdsesub1\evsprod\nda208078\0007
NA= not available (CGI assessments were not performed at baseline (Day 0); [a]p-value based on the Wilcoxon rank sum test for treatment differences. Note: Lower scores are favorable

The mean (SD) CGI-I scores on Day 4 in the low and high dose amifampridine (3.8±0.50 and 3.9±0.93, respectively) and low and high dose placebo groups (5.2±1.5 and 5.6±1.2, respectively) were comparable as well.

Reviewer's Comments: I looked at the individual SGI scoring of patients to see how their assessment correlated with clinician's assessment of improvement. The CGI scoring correlated very well with the SGI scoring of feeling worse or being satisfied with treatment effect for individual patients, adding strength to the results observed.

Exploratory Endpoints

The applicant also evaluated several exploratory endpoints that were all in favor of amifampridine (3TUG, p=0.01; Patient Evaluation of Most Bothersome Symptom, p=0.05; QMG

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Limbs Domain, p=0.001). These endpoints were not corrected for multiplicity and as such will be included in product labeling.

Conclusions

Overall, the positive results on the co-primary endpoints of Study LMS-003 provide support for the overall efficacy of amifampridine phosphate in LEMS. Discontinuation of amifampridine phosphate in the patients in a randomized withdrawal study resulted in worsening of muscle strength in the placebo group during the 4-Day treatment period. Statistically significant treatment differences in favor of amifampridine phosphate compared to placebo were observed in the co-primary endpoints, the change in QMG (p=0.0004) and SGI scores (p=0.0003) during the 4-Day double-blind and treatment phase of the study.

Statistically significant mean difference in favor of amifampridine phosphate compared to placebo was also observed for the secondary endpoint CGI-I score (p=0.002) on Day 4.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Table 20 provides an overview of the primary efficacy endpoints in the two pivotal studies, LMS-002 and LMS-003. Both studies had the same co-primary endpoints that evaluated the changes from baseline in muscle strength as assessed by change in baseline QMG score and the evaluation of the change in subject feeling about their condition as assessed by change in SGI score at the end of double blind withdrawal phase of 7 days and 4 days, respectively, for Studies LMS-002 and LMS-003. A MMRM was used to analyze each component of the co-primary endpoint for Study LMS-002 and ANCOVA for Study LMS-003.

The analyses of the primary endpoints demonstrated that improvements were statistically significantly greater for amifampridine phosphate than for placebo in patients with LEMS. Results of both studies showed that symptom worsened upon removal of amifampridine phosphate treatment.

There were statistically significant changes in QMG score (p = 0.0452) and SGI score (p =0.0028) for Study LMS-002. Study LMS-003, also demonstrated statistically significant changes in QMG score (p = 0.0004) and SGI score (p = 0.0003) as shown in Table 20. The magnitude of benefit observed in Study LMS-003 is larger than Study LMS-002.

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Table 20 Summary of co-primary endpoints in Study LMS-002 and LMS-003

Study	N	Primary Endpoints	Treatment Difference (90% CI)	P-value
LMS-002	37	QMG score	-1.7 (-3.4,-0.0)	0.0452
		SGI score	1.8 (0.7, 3.0)	0.0028
LMS-003	26	QMG score	-6.54 (-9.78, -3.29)	0.0004
		SGI score	2.95 (1.53, 4.38)	0.0003

QMG = quantitative myasthenia gravis; SGI = subject global impression

In addition, as agreed upon in the Type C (meeting minutes dated; 30 January 2018), an efficacy evaluation in the modified intent to treat (mITT) population of LMS-002 that excluded patients from the Russian Site 2007 was performed as a post-hoc analysis. These patients had the efficacy evaluations at the end of the double-blind period before the patients had received their treatments. This was a major deviation from the protocol led to lower efficacy in patients on treatment. There was statically significant treatment difference in favor of amifampridine phosphate arm (p=0.0048) when subjects (n=11) from the Russian Site 2007 were excluded in the analysis.

7.1.2. Secondary and Other Endpoints

CGI-I was the key secondary endpoint in both studies, LMS-002 and LMS-003. As summarized in Table 21, For Study LMS-002, the change from baseline in CGI-I score was statistically significant (p = 0.026) favoring amifampridine phosphate. The results from the MMRM on the change in T25FWT walking speed from baseline revealed a trend in median speed favoring amifampridine phosphate, but the results were not statistically significant (p = 0.6274), probably due to the high variability in the assessment leading to lower power to assess a treatment difference. Study LMS-003 demonstrated a significant treatment difference in favor of amifampridine phosphate (p = 0.0020).

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Table 21 Summary of secondary endpoints in Study LMS-002 and LMS-003

Study	N	Primary Endpoints	Treatment Difference (90% CI)	P-value
LMS-002	37	CGI-I score*	-1.1 (-2.1,-0.1)	0.026
		T25FWT	8.51 (-26.77, 43.79)	0.627
LMS-003	26	CGI-I score**	-	0.002

CGI-I = Clinical Global Impression-Improvement; T25FWT = timed 25-foot walk.
*Base on MMRM
** based on Wilcoxan rank sum test for treatment difference

7.1.3. Subpopulations

Age, Gender and Race:

Integrated efficacy analyses were performed with the co-primary endpoints to establish the effects of age, gender and race on the efficacy of amifampridine phosphate. For both QMG and SGI, the differences in efficacy related to age and gender cannot be reliably established. In subjects ≥65 years the LS mean difference between amifampridine phosphate and placebo was close to significance (p=0.051) for QMG, but not for SGI (p=0.315). However, the number of patients in this group in each treatment arm was very small (N=6-7) to derive meaningful conclusion in this subgroup of patients. Please refer to the subgroup analyses in Table 22 and Table 23.

In addition, there is also insufficient data in other race for any meaningful conclusion regarding efficacy across race groups.

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Table 22 Integrated Analysis of QMG in Demographic Groups

Demographic Group	Amifampridine phosphate (n = 29)	Placebo (n = 35)
Age: <65 y		
N	23	28
LS mean (SE)	0.39 (0.79)	4.14 (0.72)
LS mean difference (95% CI)	–3.75 (–5.91, –1.60)	
p-value	0.001	
Age: ≥65 y		
N	6	7
LS mean (SE)	–1.23 (1.42)	3.62 (1.29)
LS mean difference (95% CI)	–4.85 (–9.72, 0.02)	
p-value	0.051	
Sex: Male		
n	13	12
LS mean (SE)	–0.07 (0.91)	3.83 (0.95)
LS mean difference (95% CI)	–3.90 (–6.74, –1.07)	
p-value	0.009	
Sex: Female		
n	16	23
LS mean (SE)	0.39 (0.99)	3.99 (0.82)
LS mean difference (95% CI)[b]	–3.60 (–6.23, –0.98)	
p-value	0.009	
Race: White		
N	23	34
LS mean (SE)	0.28 (0.79)	4.02 (0.65)
LS mean difference (95% CI)	–3.74 (–5.80, –1.68)	
p-value	<0.001	
Race: Other		
n	5	0
LS mean (SE)	–0.40 (0.42)	Not available
LS mean difference (95% CI)	Not available	
p-value	Not available	

Source: ISE Table 5-2

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Table 23 Integrated Analysis of SGI in Demographic Groups

Demographic Group	Amifampridine phosphate (n= 29)	Placebo (n = 35)
Age: <65 y		
N	23	28
LS mean (SE)	-0.99 (0.34)	-3.37 (0.30)
LS mean difference (95% CI)	2.38 (1.46, 3.29)	
p-value	<0.001	
Age: ≥65 y		
N	6	7
LS mean (SE)	-0.09 (0.75)	-1.21 (0.69)
LS mean difference (95% CI)	1.12 (-1.24, 3.48)	
p-value	0.315	
Sex: Male		
N	13	12
LS mean (SE)	-0.49 (0.48)	-3.05 (0.50)
LS mean difference (95% CI)	2.56 (1.13, 3.99)	
p-value	0.001	
Sex: Female		
n	16	23
LS mean (SE)	-0.95 (0.44)	-2.95 (0.36)
LS mean difference (95% CI)	2.00 (0.84, 3.15)	
p-value	0.001	
Race: White		
N	23	34
LS mean (SE)	-0.94 (0.37)	-3.01 (0.31)
LS mean difference (95% CI)	2.08 (1.11, 3.04)	
p-value	<0.001	
Race: Other		
N	5	0
LS mean (SE)	0.00 (0.20)	
LS mean difference (95% CI)	Not available	
p-value	Not available	

Source: ISE Table 5-1

7.1.4. Dose and Dose-Response

Dose response cannot be determined due to the dose of amifampridine phosphate being titrated base on individual response and tolerability. The proposed starting dose for patients with LEMS is (b) (4) per day, given orally, and divided into three or four doses a day (5 to 10 mg per dose). Some patients in LMS-002 started at 15 mg per day as the protocol allowed treatment naïve patients to start at a lower dose. Doses of amifampridine phosphate were adjusted at 3- to 4- day intervals after patients have been monitored for both response and adverse events in the two studies. The total daily dose was titrated to a maximum of 80 mg per

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day (maximum single dose of 20 mg) based on the use in literature and reported benefit to the patient. The mean dose that the subjects were titrated up to in the two studies ranged from 65-75 mg per day in the treatment groups. The proposed starting and maximum doses are reasonable based on the two studies conducted, current use and doses reported in published studies. However, since Study LMS-002 enrolled treatment naïve patients and started titration on 15mg/day, the starting dose recommendation could also be ranged from 15-30mg/day. As discussed under Study LMS-002 additional dosing considerations/concerns based on concomitant administration of food, renal impairment and slow acetylators is minimal as individual doses are titrated based on tolerability and effect.

In Study LMS-003, randomization was stratified by low dose (<60 mg/d) and high dose (≥60 mg/d) of amifampridine phosphate. The applicant conducted an integrated analysis across the two studies by these dosage groups that shows a treatment difference in favor amifampridine phosphate ($p=0.001$ and $p<0.001$, respectively for QMG and SGI scores), and further supports individualized dosing for optimal effect across various stages of the disease and tolerability of patient (Table 24). I looked for trends to see if patients on doses >60mg/day perform better. There appeared to be some trend, but too few patients to make any reliable conclusions. Titrating to optimal effect is appropriate.

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Table 24 Integrated analysis of co-primary endpoints based of dosage

Primary Endpoints	Low Dose (<60 mg/d)		High Dose (≥60 mg/d)	
	Amifampridine phosphate (n = 11)	Placebo (n = 16)	Amifampridine phosphate (n = 18)	Placebo (n =19)
Subject Global Impression Score				
Mean (SD)	–0.3 (1.01)	–2.7 (2.02)	–1.0 (2.06)	–3.3 (2.40)
LS mean (SE)	–0.36 (0.48)	–2.63 (0.40)	–0.92 (0.40)	–3.33 (0.39)
LS mean difference (95% CI)	2.27 (0.96, 3.57)		2.41 (1.27, 3.55)	
p-value	0.001		<0.001	
Quantitative Myasthenia Gravis Score				
Mean (SD)	–0.4 (2.34)	3.1 (4.53)	0.6 (3.01)	4.6 (3.89)
LS mean (SE)	–0.57 (1.16)	3.27 (0.95)	0.67 (0.84)	4.47 (0.82)
LS mean difference (95% CI)	–3.84 (–6.96, –0.71)		–3.80 (–6.21, –1.39)	
p-value	0.018		0.003	

Source ISE Table 4-10

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The randomized withdrawal study design shows us that the duration and durability of the treatment effects is short. Loss of effect could be demonstrated in as little as 4 days after discontinuation of the drug in study 003. Symptoms appear to return to baseline rapidly with a missed dose and improved with a dose in the treatment phase. It is reported that patients usually perceive a benefit in 30 minutes after dosing, although the clinical trials were not designed to assess onset of effects. In addition, the short half-life of the drug (2 hours) requires dosing 3 to 4 times a day.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

None

7.2.2. Other Relevant Benefits

None

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7.3. Integrated Assessment of Effectiveness

The Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence of effectiveness if FDA determines that such data and evidence are sufficient to establish effectiveness (Section 115(a) of the Modernization Act).

With reference to 21 CFR 314.126, the overall efficacy data from two adequate and well-controlled studies submitted in the application provides for an adequate assessment of benefit supporting effectiveness for the treatment of LEMS in adults 18 years of age and older.

Study LMS-003 provides robust results across primary and key secondary endpoint. Although Study LMS-002 is less robust, the study provides support for the efficacy of amifampridine phosphate in the treatment of LEMS.

8. Review of Safety

8.1. Safety Review Approach

The applicant conducted two placebo-controlled randomized withdrawal studies in patients with LEMS:

- Study LMS-002
- Study LMS-003

The individual studies are tabulated and described in Sections 5.1, 6.1 and 6.2 in the review of clinical efficacy. Study LMS-002 consisted to 4 parts, where part 2 and 3 were the randomized discontinuation and treatment phases of 7 days each. These are described in Section 6.1 of the review. Both treatment-naïve patients and patients who had prior treatment with amifampridine were enrolled in this study. Study LMS-003 was a 4-day randomized withdrawal study that enrolled patients already treated with amifampridine phosphate from the expanded access program.

There are challenges to interpreting data from the controlled phases for use in comparative analyses for assessment of causality for AEs, vital sign changes or laboratory test results. Primarily, prior to the controlled phase, the placebo patients were treated with amifampridine phosphate and then withdrawn. This raises the concern that any AEs, vital sign changes or laboratory changes in the placebo groups during the controlled phase could reflect withdrawal from treatment rather than just the experience one would observe in the absence of treatment. Additionally, the durations of the controlled phases were too short (7 days and 4

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days, respectively) to allow for meaningful comparisons of risks. Second, both trials involved run-in phases in which all patients were exposed to amifampridine phosphate. This means that patients who participated in the controlled phases of the trials were the patients who previously demonstrated during the run-in phase that they could tolerate amifampridine phosphate at the dose studied. Third, the small number of patients participating in these trials (n=63) does not allow for robust risk comparisons.

The overall approach to safety review will be focused on descriptive summaries of the experiences of patients treated with amifampridine phosphate. The limitation of this approach is that without quantitative comparisons of risk it will be difficult to assess whether any AE, vital sign change or laboratory result was due to drug, or merely a background event that would have been observed in the absence of treatment.

Uncontrolled Safety Database:
Several sources of uncontrolled databases included:

- Study LMS-002 2-year Extension, where all patients received amifampridine phosphate
- Study LMS-002 Part 1 Run-in phase of the study

These were used in the overall assessment of common treatment-emergent adverse events in LEMS patients. Study LMS-002 Part 1 Run-in phase of the study was used to assess common treatment-emergent adverse events in treatment-naïve LEMS patients. The adverse events from treatment-naïve LEMS patients in Study LMS-002 Part 1 Run-in were found to be most informative for calculating the incidence of common adverse events to inform labeling.

Other open-label sources included:

- European LEMS Registry (EU LEMS Registry)
- Study EAP-001 (US Expanded Access Program)

The EU LEMS Registry and the Expanded Access Program (EAP-001) collected through 30, September 2017, served the purpose of evaluating serious adverse events (SAEs). The LEMS European Registry included patients on Firdapse, 3, 4 DAP and some other treatments. The LEMS Registry Annual report submitted provides a cut off of 28 November, 2015 with 96 registered with a mean time on Study of ~3 years. The Tabular Listing of Studies indicates that as of cut-off of 30 September, 2017, a total of 106 patients with LEMS are in the Registry with 78 receiving Firdapse of unknown treatment duration. The applicant notes that the patients enrolled in the registry may be on more than one treatment for LEMS, may have been taking different treatments at different times, or may be on a compounded formulation of amifampridine.

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Study EAP-001 included subjects with LEMS, congenital myasthenic syndrome (CMS), and downbeat nystagmus. A total of 139 patients have been on amifampridine phosphate in this program, with 102 patients receiving treatment for > 6 months and 77 patients for > 1 year at any dose. A total of 34 patients received doses >60 mg/day for >1 year.

These uncontrolled databases have been used for the assessment of the incidence of serious adverse events, such as seizures or cardiac arrhythmia across all exposed patients, as advised at the Pre-NDA meeting (Minutes dated 2/25/2015). The uncontrolled safety database will be considered supportive given its lack of rigor and detail of assessments.

Clinical Pharmacology Studies:
158 healthy subjects were exposed to mostly single doses of amifampridine phosphate in clinical pharmacology studies. Thirty-two subjects (8 healthy, 24 with renal impairment) were exposed to single dose of amifampridine phosphate Study in Study REN-002. Other than the QTc study, much lower single doses were administered in these studies. These were reviewed for serious AEs and discontinuations and other safety signals that were not observed in the pivotal clinical studies.

120-Day Safety Update:
The safety cut-off date for the NDA resubmission was 30 September 2017.The 120-day safety update include data from 01 October 2017 through 28 March 2018 reporting period for the EU LEMS Registry and the expanded access program EAP-001. No subjects were enrolled in the EU LEMS Registry during this period. Thirteen new subjects were enrolled in Study EAP-001 during the reporting period. The safety review includes the SAEs from these uncontrolled data and also incidences of seizures and cardiac arrhythmias.

Literature:
The sponsor provided published literature to support the safety of amifampridine phosphate. This literature was reviewed to ensure that no safety signals were missed, but the data was not used for the primary safety analyses or to establish the safety of amifampridine phosphate.

Overall Review Strategy for AEs: For the reasons stated above, the presentations of deaths, SAEs, discontinuations for AEs and TEAEs will provide the percentages of amifampridine phosphate treated patients experiencing these events, for different data groupings. The first grouping will be comprised of data from trials LMS-002 and LMS-003, which include LEMS patients, the population with the indication sought for approval. Assessment of safety in LEMS patients will be performed in the two studies individually as well (LMS-002, LMS-003) for identifying common TEAEs. The second grouping will include data from the clinical pharmacology trials that were generally single dose studies in healthy individuals. The third

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grouping will include data from supportive sources such as the US Expanded Access program (EAP-001), the European LEMS registry, and data from published studies. These data can only be considered as supportive because they are not of the same quality or detail as the data from the development program. The TEAE discussion will present one additional data grouping, those LEMS patients with no prior exposure to amifampridine phosphate at the time of enrollment in these trials (Treatment naïve patients, n=42). The value of this grouping is that the observed outcomes represent the experience for patients with their first exposure to amifampridine phosphate, the situation that clinicians and patients would encounter when initiating treatment.

Review Strategy for Vitals and Laboratory Tests: Study LMS-002 was the only study that captured laboratory data. Both LMS-002 and LMS-003 evaluated vital signs. Single dose Clinical Pharmacology studies also included assessment of laboratory tests and vital signs. The applicant did not provide analyses of these data in the Summary of Clinical Safety and referred the reader to the CSR. The CSR stated that there were no treatment related trends in mean change or shift values and provided only listing of tables for different study days in the Appendix of the report. The report does not include a discussion of any outliers observed and the assessment of its clinical significance.

I reviewed the raw laboratory test and vital sign data. Limitations related to the study design and the small number of subjects, do not support the usual NDA review laboratory data analyses. Comparisons of mean changes or abnormally low/high results for the short controlled phase are difficult to interpret. Therefore, I have focused my analyses on identification of potentially clinically significant (PCS) laboratory and vital sign results occurring during the study.

Vital sign and laboratory data analyses will not follow the same groupings since all trials did not include similar data collection. Clinical pharmacology studies were also reviewed for outliers in laboratory tests and vitals. Outliers will be assessed graphically in JMP/JMP Clinical using potentially significant criteria based on Attachment B of Clinical Template and the Common Terminology Criteria for Adverse Events (CTCAE) grade 1 criteria. For each patient who met PCS criteria, I summarize the observed results and discuss whether any of these results were considered an AE.

Review Strategy for Safety issues of Special Interest: Safety issues of interest that the applicant includes in the product label include:

- Seizures
- Cardiac disorders

Seizures is also included in another approved aminopyridine, AMPYRA® (dalfampridine), in the Warnings and Precaution section of the label; however, Cardiac Disorders are not. Given that amifampridine phosphate is a voltage-gated potassium channel blocker, the applicant considers

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that there is potential for it to be arrhythmogenic. These occurrences of these AEs of interest are reviewed from the applicant's overall development program, from the Expanded Access Program and the LEMS European Registry. Narratives regarding these AEs was reviewed and included in this review as necessary.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Given that amifampridine is intended for an orphan indication, the exposure in the development program is understandably far less than that recommended by the ICH guidelines. However, since LEMS is a rare disease, there is no specific minimum number of patients that should be studied to establish clinical safety.

The main safety data of amifampridine phosphate was generated from the two double-blind randomized withdrawal studies (LMS-002 and LMS-003) in 79 adults with LEMS. Only 63 of the patients enrolled participated in the controlled part of the study in both studies. Since the two studies were conducted several years apart, Study LMS-003 allowed enrollment of subjects who previously participated in Study LMS-002. There were 9 subjects that participated in both studies. Study LMS-002 had an open-label Run-In Phase (Part 1) where 54 subjects were enrolled. A total of 42 of these were treatment-naïve patients. A total of 37 subjects out of 54 were randomized to the controlled part of the study (Part 2 and 3). All enrolled subjects continued into the open-label extension (Part 4), unless they discontinued the study. No new subjects were enrolled in the extension study.

The data from the controlled part of Study LMS-002 (Part 2 and 3, 14 days total) and entire LMS-003 (4 days) constitute the controlled safety database. As previously noted, the controlled database was of very short duration.

The majority of the long-term safety assessment comes from the open label parts of Study LMS-002 (a 7 to 91 day Run-In; Part 1 and open label extension up to 2 year; Part 4). As defined, the safety population included all subjects who received ≥ 1 dose of Amifampridine.

The safety population included 53 enrolled patients who received at least 1 dose of amifampridine and had any posttreatment safety information collected. Patient (b) (6) was enrolled, but did not have any post baseline data, so this patient was not included in the safety population (Note: A total of 54 were enrolled initially).

A total of 13 individuals with LEMS were exposed to amifampridine for 4 days in trial LMS-003. Three of these individuals also participated in LMS-002.

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In addition, there were a total of 166 healthy subjects (includes 8 patients that were in the renal study) and 24 renally impaired patients that were exposed to amifampridine phosphate in Clinical Pharmacology Studies. In these studies subjects were mostly exposed to single dose of amifampridine phosphate. Only one study administered multiple doses for <4 days.

The European LEMS Registry and the US expanded-access Study EAP-001 collected through 30 September 2017 informed adverse events of special interest, such as deaths, seizures, cardiac disorders. The exposures from these sources are provided in Table 25 when available.
The summary of overall exposure is provided in Table 25.

Table 25 Overall Exposure of Amifampridine Phosphate

Total unique subjects exposed to amifampridine phosphate N= 475			
	Unique Subjects	Total Subjects	
Controlled studies			
LMS-002 LMS-003	**53**[d] 17	53[a] 26[b]	Total 17 unique out of 26, 10 unique on drug
Open-label extension			
LMS-002 Ext		40[c]	
Healthy Subjects	**166**		
LMS-001 FIR-001 QTC-002 DAPSEL REN-002		47 26 58 27 8	
Renally Impaired Subjects	**24**		
REN-002		24	
EU LEMS Registry	**76**	105 with 76 on Firdapse	
Expanded Access EAP-001	**139**	139[e] 85 LEMS Patients	

[a]37 subjects of 53 enrolled were randomized to the controlled part 3 of the study
[b]9 out of 26 subjects also participated in Study LMS-002 prior to enrollment in Study LMS-003
[c]Includes subjects who rolled over from Part 1, 2, or 3
[d]54 were enrolled, but one patient did not have any post baseline assessment, hence only 53 were included in the safety population
[e]Includes patients with LEMS, congentital myasthenic syndrome (CMS) and Downbeat nystagmus (DBN)

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Amifampridine doses administered ranged from 30-80 mg/day. The duration of exposure at each dose from the controlled study and the Expanded Access Study EAP-001 is summarized in Table 26. A total of 40 subjects (63%) had >6 months of exposure to amifampridine phosphate at any dose. A total of 39 (62%) subjects had >12 months of exposure at any dose. 25 subjects (40%) had >12 months of exposure at doses >60 mg.

Table 26 Duration of Exposure

	Number of patients exposed to the amifampridine phosphate n(%)				
	Dosage	1-7 days	>6 months	>12 months	>18 months
LMS-002 and LMS-003 Double blind treatment period N=28					
	<30 mg/day	0 (0%)	-	-	-
	30-60 mg/day	14 (50%)	-	-	-
	>60 mg/day	14 (50%)	-	-	-
	Any Dose	27 (100%)	-	-	-
All LMS-002 and LMS-003 N=63					
	<30 mg/day	0 (%)	1 (2%)	1 (2%)	1 (2%)
	30-60 mg/day	5 (8%)	14 (22%)	13 (21%)	11 (17%)
	>60 mg/day	5 (8%)	25 (40%)	25 (40%)	24 (38%)
	Any Dose	10 (16%)	40 (63%)	39 (62%)	36 (57%)
Expanded Access Study EAP-001 N=139					
	<30 mg/day	0	10 (7%)	4 (3%)	1 (<1%)
	30-60 mg/day	0	52 (37%)	39 (28%)	24 (17%)
	>60 mg/day	0	40 (29%)	34 (24%)	28 (20%)
	Any Dose (N=139)	0	102 (73%)	77 (55%)	53 (38%)

Source: Section 5.3.5.3 ISS Appendix A, Table 3.1 and 3.2 and EAP-001 Attachment A
Note: For the controlled studies only 40 patients of the 63 entered open-label phase. For the expanded access, exposure data is available for 139 subjects

In LMS-002 Extension Part 4, 40 subjects were exposed to the study drug at a mean daily dose of 66 (± 18) mg for a mean duration of 785 (± 310) days.

In LMS-003, 26 subjects were exposed to a mean total daily dose of 60±20 mg for the amifampridine phosphate group, and 63 ±19 mg for the placebo group during the 4-day randomized period.

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The overall duration of exposure from the Clinical Pharmacology studies was <4 days. Most of the studies were single dose studies. A total of 100 (64%) healthy subjects received doses <30 mg/day of amifampridine phosphate. A total of 58 (37%) healthy subjects received doses between 30-60 mg/day of amifampridine phosphate.
In Study EAP-001 at total of 52 (61%) LEMS patients were <65 years of age and 33 (39%) patients were >65 years of age. The median (SD) number of days in the study is 464 with a range of 28-1024 days. The mean daily dose in the LEMS patients is 56mg/day (range 9-136 mg/day).

The duration of dosing for the EU LEMS Registry is not available.

8.2.2. Relevant characteristics of the safety population

There were 54 unique subjects in the controlled studies LMS-002 and LMS-003. The demographic characteristics of both studies combined are summarized in Table 27. Baseline characteristics were generally similar across treatment groups.

Table 27 Summary of Demographics in Study LMS-002 and LMS-003

Parameter	Statistic	Amifampridine (N = 26)[a]	Placebo (N = 28)[a]
Age (years)	Mean (SD)	52 (12)	50 (15)
	Median	53	54
	Min., max.	25, 71	21, 69
Gender	Male	12 (46%)	10 (36%)
	Female	14 (54%)	18 (64%)
Race	White	22 (88%)	27 (100%)
	Black	1 (4%)	0
	Other	2 (8.0%)	0
	Missing	1	1
Ethnicity	Hispanic or Latino	4 (19%)	1 (4%)
	Not Hispanic or Latino	21 (77%)	27 (96%)
	Not reported	1 (4%)	0
Height (cm)	Mean (SD)	171 (10)	167 (11)
	Median	170	165
	Min., max.	153, 194	153, 188
Weight (kg)	Mean (SD)	82 (19.926)	76 (19)
	Median	80	74
	Min., max.	56, 130	48, 133
BMI (kg/m^2)	Mean (SD)	28 (5)	27 (5)
	Median	27	26
	Min., max.	21, 40	20, 40

[a]Subjects that participated in both Study LMS-002 and Study LMS-003 were counted once based on the randomization assignment for Study LMS-002.

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The summary of demographics from the 76 subjects in the EU LEMS registry and EAP-001 is shown in Table 28. The demographics of the EU Registry and EAP-001 is similar the controlled studies.

Table 28 Summary of Demographics in EU LEMS Registry and EAP-001

	EU LEMS Registry		EAP-001
Demographic	Firdapse (n =48)	3,4-DAP (n=28)	Firdapse (n =85)
Age (years)			
Mean (SD)	60 (11)	61 (13)	59 (16)
Minimum-maximum	24-81	38-84	10-92
Sex			
Male	25 (52%)	16 (57%)	28 (34)
Female	23 (48%)	12 (43%)	56 (66)
Race			
Caucasian	32 (67%)	21 (75%)	76 (89%)
Black	0 (0%)	0 (0.0%)	6(7%)
Asian	0 (0%)	1 (4%)	1 (1%)
Hispanic	0 (0%)	1 (4%)	0 (0%)
Other	11 (23%)	5 (18%)	2 (2%)

Adapted from 120-day safety update

8.2.3. Adequacy of the safety database

The exposure in the development program is understandably far less than that recommended by the ICH guidelines. However, because amifampridine phosphate is intended for an orphan indication, the development program is adequate.

Based on the characteristics provided in Table 27 and Table 28, the majority of the patients were White. The studies enrolled 1 Black patient and 2 patients of other Race. It is not known whether the course of LEMS differs in the minority populations. There is adequate experience on both genders.

Given the orphan nature of the disease, the patient exposure appears adequate and generalizable to the US population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

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The applicant's narratives in the original submission lacked details in many cases. There were also discrepancies identified between information/laboratory values provided in the narratives and those in the databases. There were narratives that were missing or included in different sections of the application that affected the ability to perform the review. The applicant rectified these issues during the review period promptly.

The application did not include any outlier analyses or summary tables in the Integrated Summary of Safety for the laboratory tests, vitals and ECGs. The reviewer was referred to the study reports for these. The individual study reports also did not provide these summary tables or a discussion of any findings, but referred the reader to the Appendices of Tables for review the Line Listings.

The frequencies of safety assessments were adequate in both studies. For Study LMS-002, the safety assessments were conducted bi-weekly (q2 weeks) in the open label run in phase, at Day 1, 8 and 14 of the Double-Blind Phase and quarterly for the 2-year open-label extension of the study and at Study Termination. Study LMS-003 was a short withdrawal study with safety assessments at baseline and Day 4. Laboratory and ECG assessments were not conducted in this study.

8.3.2. Categorization of Adverse Events

The applicant's process of recording AEs was appropriate. All patients who received at least 1 dose of IP (amifampridine phosphate or placebo), and had any posttreatment safety information collected were included in the safety analysis. Only treatment-emergent AEs (TEAEs) were included in the safety analysis. A TEAE was defined as an AE that emerged during treatment, having been absent pretreatment, or that worsened relative to the pretreatment state. In counting the number of AEs reported, a continuous event (i.e., an AE reported more than once and which did not cease) was counted only once with the worst-recorded severity; non-continuous AEs reported several times by the same patient were counted as multiple events. Events present immediately prior to the first dose of study drug during Part 1 of the study that did not worsen in severity, were not included. The investigators were asked to categorize adverse events as mild, moderate, or severe based on Common Terminology Criteria for Adverse Events (CTCAE) v 4 grades. In deriving the tabulation relating to preferred term reporting, the severity of a recurrent AE was taken to be the most severe and the relationship to study drug as the most probable within the study. Investigators also assigned the causality of the AE as not related, possibly related and probably related. However, these had no bearings in the assessment AE frequencies.

Adverse events were coded to MedDRA 13.1. The verbatim terms were manually reviewed for accuracy of coding. The applicant's coding resulted in appropriate translation of verbatim terms to preferred terms. However, AEs were often coded to multiple different equivalent Preferred

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Terms. The grouping of closely related terms or pooling of preferred terms was not accurately conducted by the applicant.

For example, the applicant had used several preferred terms that indicated elevated liver enzymes as an AE. "Elevated liver enzymes" was also a preferred term of the applicant. I regrouped the other terms such as "Alanine aminotransferase increased", "Aspartate aminotransferase increased", "Blood lactate dehydrogenase increased', "Gamma-glutamyl transferase increased', "Hepatic enzyme increased" as "Elevated liver enzymes". Other terms that were pooled are given in Table 29. I performed the safety analyses after pooling the applicant's preferred terms for several TEAEs as indicated in Table 29. By regrouping, the frequencies of certain AEs given in Table 29 were increased, as expected.

Table 29 Pooling of preferred Terms by the Reviewer

Preferred Terms of the Applicant	Pooled Terms by the Reviewer
Elevated liver enzymes, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood lactate dehydrogenase increased, Gamma-glutamyl transferase increased, Hepatic enzyme increased	Elevated Liver Enzymes
Upper respiratory tract infection, Nasopharyngitis, Sinusitis, Rhinorrhea, Chronic sinusitis, Pharyngitis, Respiratory tract infection viral, Nasal congestion	Upper respiratory Tract infection
Paresthesia, Paresthesia oral, Hypoesthesia oral	Paresthesia
Muscle Spasm, Muscle contractions involuntary, Muscle twitching	Muscle Spasm
Fatigue, Asthenia	Asthenia
Erythema, Contact dermatitis, dermatitis	Erythema
Abdominal pain, Abdominal pain upper, Abdominal discomfort, Abdominal distension	Abdominal Pain
Anal fissure, Rectal hemorrhage	Anal fissure
Balance Disorder, Gait Disturbance	Balance Disorder
Feeling of body temperature change, Feeling hot, Feeling cold	Feeling of body temperature change
Insomnia, Insomnia exacerbated, Sleeplessness	Insomnia
Dyspnea, Shortness of breadth	Dyspnea

In addition, to the pooling of similar terms, I also had to regroup similar events in the primary system organ class (SOC). For example, since I grouped all "Paresthesia", "Paresthesia oral" and "Hypoesthesia oral" as "Paresthesia", I had to put them all in the Nervous system disorder SOC instead of Gastrointestinal Disorders SOC for the oral hypoesthesia. Similarly, "Upper

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Respiratory Tract Infections" were split under Infections and Infestations SOC and Respiratory, thoracic and mediastinal disorders SOC. These were all grouped under Infections and Infestations SOC. In addition "muscle spasm" was listed under Musculoskelatal and Connective tissue disorder SOC. I grouped the terms "muscle spasm", "Muscle contractions involuntary", "Tremor", "Muscle twitching" under Nervous System disorder SOC.

8.3.3. Routine Clinical Tests

Routine clinical tests included hematology, chemistry and urine analysis parameters and Vital Signs were only assessed in Study LMS-002 bi-weekly (q2 weeks) in the open label run in phase, at Day 1, 8 and 14 of the Double-Blind Phase and quarterly for the 2-year open-label extension of the Study and at Study Termination. In the event of serious AEs, safety laboratory tests could be obtained at investigator's discretion. The Laboratory values were based on Common Terminology Criteria for Adverse Events (CTCAE) v 4 grades. There was no indication that any tests were conducted under fasting conditions. The reference range of some laboratory tests differed amongst laboratory tests. These were taken into consideration when evaluating outliers. Given that the half-life of amifampridine phosphate is <2 hours, obtaining peak or trough vitals was not necessary. The sponsor did not provide any shift tables or outlier tables and provided no discussion of any outliers. I evaluated outliers for each test individually graphically in JMP/JMP Clinical using potentially significant criteria provided in Attachment B I of Clinical Review Template and the CTCAE. There were no significant missing values that could impact the overall assessment of the routine clinical tests. There were only 3 missing values for erythrocyte cell morphology. Overall the assessment methods appeared reasonable.

8.4. Safety Results

8.4.1. Deaths

<u>LMS-002, LMS-002 Extension and LMS-003</u>
One death occurred during Part 4 of LMS-002 Extension, Part 4. A 60-year-old white female patient died as a result of small cell lung cancer. The death was confounded due to the underlying disease, and hence, it is difficult to attribute death to amifampridine phosphate.

No deaths occurred during Study LMS-003.

<u>Clinical Pharmacology Studies:</u> No deaths occurred in these studies.

<u>EU LEMS Registry and EAP-001:</u>
15 deaths were reported out of 215 patients in the EU LEMS Registry and Study EAP-001 for patients treated with amifampridine. The causes of death were given as summarized in Table 30. The cause of death in many LEMS patients was confounded due to the underlying cancer

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and likely the cause of death. About 50-60% of LEMS patients have cancer, usually small cell lung cancer, and it is typically the cause of death in these patients. In addition, many patients were much older with multisystemic disease, hence it is difficult to attribute the deaths to amifampridine phosphate. Conversely, it also cannot be said that none of these deaths were due to amifampridine phosphate. Several cases lacked the details to assess causality of death. The case of aspiration bronchial was considered possibly related to medication being taken for LEMS by the applicant. All other cases were considered unrelated by the applicant. Not all narratives were provided. A request was made during the review cycle, but the applicant provided all available information and a few narratives remained missing. Reviewer's comments regarding cause of death are given in Table 30 where applicable.

Table 30 Cause of Death

Preferred Term for Cause of Death	Reviewer's Comment on Cause of Death
Small cell lung cancer stage unspecified	Patient was 67-year-old person (gender unknown), who did not have small cell lung cancer before initiation of amifampridine phosphate. Dosing was initiated at 35 mg QD and reduced to 10 mg QD a year later. Patient was diagnosed with pneumopathy/candida pneumonia of moderate severity and developed severe small cell lung carcinoma that progressed. Death likely due to underlying cancer.
Small cell lung cancer stage unspecified	A 63-year-old female with a history of small cell lung cancer developed severe small cell lung cancer. Death likely due to underlying cancer.
Small cell lung cancer stage unspecified	No narrative provided. Death likely due to underlying cancer.
Lung neoplasm malignant	Patient was a 57-year-old male with lung neoplasm malignant, metastases to central nervous system and LEMS. Patient was on 20 mg TID amifampridine phosphate. Death likely due to underlying cancer.
Cardiac arrest	Patient was a 59-yearold female with no history of cardiac disorder who was on 3,4 DAP for 6 months. Dose at time of death is not reported. 3, 4 DAP was initiated at 15 mg QID. Lack of information precludes any assessment of the cause of death. 3,4 DAP is amifampridine base and essentially the same active moiety as in amifampridine phosphate.
Cardiac arrest	Patient was a 75-year-old female with concurrent lung cancer. Past medical history and concomitant medications unknown. This subject died within 40 days of initiating 3, 4 DAP (same active moiety) at a dose of 20 mg TID. No laboratory or diagnostic tests or clinical details reported. The investigator notes that the other possible etiological factors that could have caused the death include lung cancer and metastasis.

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Acute coronary syndrome	Patient was a 73-year-old male. Detailed narrative summarized below the Table.
Acute myocardial infarction	Patient was 93-year- old with history of pacemaker and TIAs. Most recent dose was 80 mg. Study drug was discontinued 3 days prior to death due to dysphagia. The number of years on amifampridine is not known. Patient was elderly with predisposed cardiovascular risk factors.
Respiratory failure, Pneumonia aspiration, Seizures	Patient was a 87-year-old female. Detailed narrative of this case is summarized below the Table.
Pneumonia aspiration	Subject was enrolled in EAP, but died before any medication, had medical history of small cell carcinoma of the lungs.
Respiratory arrest	Patient was a 58-year-old male with small cell lung cancer that experienced severe respiratory arrest and died. No additional clinical information was provided. No laboratory or diagnostic tests were reported. The cause of death was reported as progression of small cell lung cancer.
Aspiration bronchial	Patient was a male of unspecified age. Detailed narrative of this case is summarized below the Table.
Pseudomonas infection	No narrative provided.
Renal failure	No narrative provided.
Amyotrophic lateral sclerosis	A 66-year-old female experienced increased difficulty in breathing and generalized weakness. Most recent dose was 30 mg prior to the event. The subject died about 40 days after this dose. It is unclear from the narrative if subject was taking amifampridine prior to the death. Death likely due to underlying disease of ALS.
Cardiac arrest (included in 120-day safety update)	46-year-old female with a history of cardiac conditions (noted below) prior to beginning amifampridine treatment experienced cardiac arrest and died approximately 1 year and 4 1/2 months after beginning treatment. The most recent dose was 80 mg prior to the event. Cardiac related issues included complete heart block non-ischemic cardiomyopathy biventricular cardiac pacemaker placement (b) (6), automatic implantable cardioverter defibrillator and congestive heart failure. Death likely due to underlying cardiac conditions.

Source Adapted from ISS Appendix A, Table 4.2

Narratives of cases that have more detailed information and of interest are summarized below:

Case: Pneumonia aspiration; Seizure; Sepsis; Respiratory Failure
Patient was a 87-year old female with a medical history of hypertension, hypothyroidism, pernicious anemia, cholecystectomy, appendectomy, COPD, TIA, atrial fibrillation, congestive heart failure. The most recent dose of amifampridine phosphate reported was 50 mg. After 466 days on treatment with amifampridine phosphate, the patient was hospitalized for high fever,

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chills, activity change, appetite change, shortness of breath, nausea, and light-headedness. Broad-spectrum antibiotics were started for pneumonia (right lower lobe pneumonia) and sepsis. Sepsis was thought to be secondary to right lower lobe pneumonia and leukocytosis and eventually resolved after 3 days. After about 2 months, the patient began experiencing seizures and was admitted to the hospital. The patient was started on levetiracetam and the seizures resolved. EEG was negative for epileptic foci. (Please refer to Section 8.5.1 for a more detailed discussion of the seizure event). At this time, the patient was also diagnosed with a urinary tract infection, pneumonia, and sepsis. Patient was discharged a week later. About three weeks after that hospitalization, the patient was placed in hospice care and died a day later. No autopsy was done, but cause of death was attributed to respiratory failure. The patient was on amifampridine phosphate for 1 year and 6 months prior to this event.

Death due respiratory failure could be related to the recent diagnosis of pneumonia and sepsis. While seizures could be secondary to sepsis, given the known risk of seizures with aminopyridines, the attribution of amifampridine phosphate to seizures cannot be ruled out.

Case: Aspiration bronchial

The patient's concurrent conditions included LEMS, ischemic coronary heart disease, hypercholesterolemia, Hodgkin's lymphoma, arterial hypertension and post-anoxic encephalopathy. The subject had no history of smoking. The patient initiated treatment with amifampridine phosphate (10 mg, TID). The dose was increased to 10 mg QID in the subsequent week. The patient was also taking Lyrica (pregabalin), Perfalgan (paracetamol) and Contramal (tramadol) for the indication of LEMS. On the day that the patient’s dose was increased to 10 mg QID, the patient experienced severe bronchial aspiration. Four days later, a nurse discovered the patient with cyanosis and bradycardia (28 beats per minute). The patient's initial oxygen saturation level was 35%. He was treated with epinephrine and admitted to the resuscitation unit where he was treated with norepinephrine. During the first 24 hours, the patient was treated with midazolam and sufentanil. He remained in a hypothermic condition with no arousal. After an additional 10 days, the results of an electroencephalogram were consistent with severe anoxic encephalopathy. A multidisciplinary decision was made to extubate the patient. Three days later, the patient died with a final diagnosis of post anoxic encephalopathy caused by severe bronchial aspiration. The investigator assessed the event of bronchial aspiration as possibly related to treatment with amifampridine phosphate and possibly related to the subject's additional LEMS treatment medications Lyrica (pregabalin), Perfalgan (paracetamol) and Contramal (tramadol). As the patient had several serious medical conditions, it is difficult to assess if amifampridine phosphate alone contributed to the patient’s death.

Case: Acute Coronary syndrome

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A 73-year old male with LEMS experienced acute coronary syndrome while being treated with amifampridine phosphate. The subject's past medical history was significant for esophageal adenocarcinoma, gastric tumor, left middle cerebral artery ischemic stroke, prostate cancer, prostatectomy, previous cigarette smoking, epidermoid carcinoma of the left vocal cords, prostatic adenoma. The subject's concurrent conditions included myasthenic syndrome, small cell lung cancer with metastases to the liver and bone, hypertension, emphysema, dyslipidemia, hypercholesterolemia.

The patient initiated treatment with 80 mg QD amifampridine phosphate. In addition, the subject was also treated with prednisolone (7 mg, qd), pyridostigmine bromide (60 mg, qid), and intravenous immunoglobulin (160 g, q4w). After 4 years and 3 months on Firdapse, the patient experienced severe acute coronary syndrome with cardiogenic shock. He had a 3-day history of chest tightness and experienced signs of dyspnea while hospitalized in the oncology department for treatment of his lung cancer. No apical thrombus was seen. There was no aortic vascular disease. LVFPs were high. LV was dilated to 62 mm. RV was not dilated. IVC was at 2 cm. Pericardium was dry. Small right pleural effusion was noted. A chest X-ray showed pulmonary overload. Laboratory test results included troponin 3,371 ng/L, BNP 172 ng/L, leukocytes 6,400/mm3, CRP 62 mg/L, hemoglobin 13.9 g/dL, platelets 246,000/mm3, urea 7.7 mmol/L, sodium 125 mmol/L, potassium 4.1 mmol/L, and blood gas results of pH 7.34, pO2 82 mmHg, pCO2 32 mmHg, and bicarbonates 17 mmol/L. The subject was considered to have ST elevation acute coronary syndrome with heart failure. The action taken with Firdapse, prednisolone, pyridostigmine bromide, and immunoglobulin due to the event was not reported. It was not reported if an autopsy was performed.

Given that the patient was on amifampridine phosphate for about 4 years prior to the event, there is not a strong temporal relationship with the event to the drug. The patients known cardiovascular risk factors and underlying cancers likely contributed to the cardiac death.

In conclusion, it does not appear appropriate to attribute any of the deaths in the development program to amifampridine phosphate. The casualties are confounded by comorbid conditions and LEMS disease.

8.4.2. Serious Adverse Events

<u>Studies LMS-002 and LMS-003:</u>

For Study LMS-002, three serious adverse events of respiratory failure, pulmonary embolism and exacerbation of urolithiasis (renal colic) were reported during the open-label Run-In Part 1 of the study. Brief narratives of these cases are as summarized below. Conclusive correlation to drug could not be determined. The patient experiencing exacerbation of urolithiasis had a

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significant medical history of urinary calculus; therefore, the event is considered unrelated to treatment.

No SAE's were observed in the controlled parts (Part 2 and 3) of the study. During the 2-years long term open-label extension Part 4 of Study LMS-002, 23 SAEs were reported in 10 subjects. Four SAEs of elevated hepatic enzymes were observed which could be considered related to amifampridine phosphate. Two of these were in the same subject at different timepoints. However, only one patient, had an increase in ALT, AST and GGT that were >3XULN at only one instance in the open label extension phase. These cases are described in section 8.3.6 Laboratory Findings.

The remaining 19 SAEs included: cataract, macular degeneration, glaucoma, viral infection, sick sinus syndrome, lung neoplasm malignant, small cell lung cancer, fall, asthenia, myasthenic syndrome, urinary tract infection, mental status change, diarrhea, gastroenteritis, cardiac failure congestive and sinus bradycardia. Most SAEs, except for macular degeneration and lung neoplasm malignant, were resolved. None required dose modification. The SAE of small cell lung cancer was fatal. The SAEs appeared to occur in patients with predisposed risk factors for the AEs, hence no conclusive temporal relation to amifampridine phosphate can be drawn. Amongst all the SAES, only cataract and elevated liver enzyme was reported in more than one subject.

No SAEs reported were reported for Study LMS-003.

Case: Respiratory Failure
A 41-year old male had respiratory failure that required hospitalization. The patient was treatment-naïve and experienced respiratory failure 112 days post dose in the open label run-in in phase and was receiving amifampridine phosphate 80 mg/day at the time of the event. The patient was titrated up to 80 mg/day. About one week prior, (Day 105 post enrollment), the patient experienced upper respiratory tract symptoms, including shortness of breath, with feeling of fever (temperature not taken). Day 112 post enrollment, he was seen by a physician for possible sinus infection and headache. One dose of Levaquin (levofloxacin) was given. The patient was hospitalized for life-threatening respiratory failure. Negative inspiratory force (NIF) was 0, and the patient was emergently intubated. Arterial blood gases (ABGs) revealed that he was retaining CO2; an arterial line was placed to monitor. Body temperature revealed low grade fever of 100.9 degrees Fahrenheit. Urinalysis and chest x-ray revealed no indication of infection; blood cultures were negative. Concomitant medications included 60 mg/day Mestinon (pyridigostigmine bromide), 15 mg/day prednisone, and Imuran (azathioprine sodium). Mestinon (pyridigostigmine bromide) and prednisone dosages were increased, and oral potassium chloride was given due to hypokalemia. The patient was extubated without complications. Albuterol nebulizers were given as needed. NIF increased to -60. He was treated

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with intravenous immunoglobulin (IVIG) over three days due to continued difficulty with ambulation, and rising from sitting to standing. Study drug was discontinued. Other medications during hospitalization included paracetamol, diphenhydramine, docusate sodium, famotidine, milk of magnesia, senna extract, insulin aspart, and heparin. A secondary diagnosis of asthma was made by the investigator. The event was considered recovered/resolved. Attribution of respiratory failure to drug is unclear. However, respiratory failure is known to occur in LEMS. It appears that a respiratory infection may have precipitated a worsening of the patient's LEMS.

Case: Pulmonary embolism
A 75-year-old female with a significant history of hypertension, cardiac murmur, diabetes and anemia began the Run-in Phase with a 30 mg dose of amifampridine phosphate that was incrementally titrated 60 mg in 3 months. After 5 days of starting the run in phase, the patient reported a serious adverse event of pulmonary embolism and was hospitalized. The event was assessed by the investigator as moderate and as unrelated to study drug. The study drug was interrupted and the adverse event was considered recovered/resolved is 3 days. Subsequently, the patient received 40 mg amifampridine phosphate before treatment was disrupted. A month later, the patient was withdrawn from the study due to physician decision due to the complexity of her case due to comorbid conditions (particularly diabetes), her lack of compliance, and pronounced weakness in her legs. The event of pulmonary embolism appears to be unrelated to the drug.

Case: Exacerbation of urolithiasis (renal colic)
A 25-year-old female ongoing medical history of calculus urinary has exacerbation of urolithiasis. This event is unrelated to amifampridine phosphate.

Clinical Pharmacology Studies:

No SAEs were reported.

Uncontrolled Studies

From EU LEMS Registry and EAP-001, 45 patients reported at least one SAE out of a population of 202 patients between the two studies (Note: This does not include the 13 new exposures reported in the 120-day safety update of the application). The most frequently reported preferred terms were asthenia (5 patients, 2.0%), respiratory failure or acute respiratory failure (4, patients, 1.8%), cardiac arrest or cardiac failure (4, patients, 1.8%), and small cell lung cancer stage unspecified (4 patients, 1.8%). Seizures were reported in 2 patients (0.9%).

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Summary of SAEs from the EU LEMS Registry and EAP-001 reported for two or more patients is summarized in Table 31. Asthenia, small cell lung cancer and respiratory failure[1] are likely associated with the disease. Seizures could possibly be associated with the use of amifampridine phosphate.

Table 31 SAEs from the EU LEMS Registry and EAP-001 in 2 or more patients

Preferred Term	# of AEs N = 202 n (%)
Asthenia	5 (2.5%)
Respiratory failure, acute respiratory failure	4 (2%)
Cardiac arrest, cardiac failure	4 (2%)
Small cell lung cancer stage unspecified	4 (2%)
Pneumonia aspiration	2 (0.9%)
Metastases to central nervous system	2 (0.9%)
Condition aggravated	2 (0.9%)
Seizure	2 (0.9%)

Source: Adapted from ISS Appendix A

The 120-day safety update did not include any new SAEs. Two cases of seizures (one new patient, one recurrence) were observed, which are described in section 8.4.4.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were 7 discontinuations from Study LMS-002 due to adverse events. No subject discontinued from Study LMS-003 discontinued due to an adverse event. The reasons for discontinuations were:

- respiratory failure (Run-in phase, 112 days post enrollment on 80 mg/day)
- abdominal pain, diarrhea and vomiting (Run-in phase, 60 days post enrollment on 40 mg/day)
- Fatigue, laziness, involuntary muscle contractions, paresthesia (Run-in phase, 1 day post enrollment on 30 mg/day)
- Abdominal pain (Run-in phase, 24 days post enrollment on 20 mg/day)
- Alanine aminotransferase increase (open label extension phase, 736 days post enrollment on 80 mg/day)
- Small cell lung cancer (open label extension phase, 520 days post enrollment on 80 mg/day, patient dies at 586 days post enrollment)

[1] Nicole ML et al, Lambert Eaton mayasthenic syndrome associated with severe respiratory failure, muscle nerve 19(10), 1328, 1996

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- Sinusitis (Run-in phase, CRF was not specific of TEAE with discontinuation)

Except for the small cell lung cancer, all other events resolved on discontinuation of treatment.

Two subjects discontinued from the clinical pharmacology studies due to:
- Gastroenteritis
- Hepatic enzymes increased (See Section 8.4.6)

8.4.4. Significant Adverse Events

There were 16 severe AEs in the development program that occurred in 11 subjects. The severe AEs included asthenia/fatigue (n=4), diarrhea (n=2), and single occurrence of vomiting, dry mouth, abdominal pain, muscular weakness, fall, gait disturbance, worsening of macular degeneration, osteoporosis, lung neoplasm malignant, and small cell lung cancer. Except for macular degeneration, lung neoplasm malignant and small cell lung cancer, all others were resolved during the study.

One patient on 37 mg amifampridine phosphate had abdominal pain, diarrhea and vomiting and had the drug withdrawn. For all other severe AEs, there was no change in the dose of amifampridine phosphate.

Amongst these severe AEs, abdominal pain, diarrhea, vomiting and dry mouth could be drug related. Many of the other severe AEs appear related to LEMS indication.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study LMS-002 and LMS-003:
As discussed under Review Strategy, the common TEAEs from the double-blind phase of the controlled studies LMS-002 and LMS-003 is not very informative. For withdrawal study designs, the AEs observed may be due worsening of the underlying disease symptoms from the withdrawal of treatment rather than due to treatment, as seen in below in Table 32 . In both studies with double-blind period of 7and 4 days respectively, the placebo group had larger number of adverse events.

Table 32 Treatment-Emergent Adverse Events in the Double-Blind Phase of LMS-002

AE Preferred Term	Placebo N=21	Amifampridine Phosphate N=16
Otitis externa	.	1(6.3%)
Periodontitis	1 (4.8%)	.
Pulpitis dental	1(4.8%)	.

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AE Preferred Term	Placebo N=21	Amifampridine Phosphate N=16
Upper respiratory tract infection	.	1(6.3%)
Urinary tract infection	.	1(6.3%)
Muscular weakness	1(4.8%)	.
Sensation of heaviness	1(4.8%)	.
Asthenia	2 (9.5%)	.
Blood creatine phosphokinase increased	1(4.8%)	.
Depression	1(4.8%)	.
Dyspnea	1(4.8%)	.

Similarly, in the double-blind phase of Study LMS-003, more AEs were observed in the placebo arm compared to the amifampridine phosphate arm. TEAEs that occurred in 2 or more patients are given in Table 33. A total of 10 patients in the placebo group reported a total of 50 TEAEs. There were also three TEAEs occurring in one patient each observed in the amifampridine phosphate arm (back pain, pain in the extremity, and headache). The majority of TEAEs that occurred in the placebo arm appear to be due to worsening of the underlying disease due to withdrawal of treatment.

Table 33 Treatment-Emergent Adverse Events in LMS-003 occurring in 2 or more patients

AE Preferred Term	Placebo N=13	Amifampridine Phosphate N=13
Dry mouth	2 (15%)	.
Fatigue	4 (31%)	.
Asthenia	2 (15%)	.
Feeling Hot	2(15%).	.
Muscular Weakness	5 (39%)	.
Muscle Spasm	2 (15%)	.
Limb discomfort	2 (15%)	.
Balance Disorder	2 (15%)	.

All treatment emergent adverse events (TEAEs) that occurred in > 5% of the patients in Studies LMS-002 and LMS-003 on amifampridine phosphate <u>without regard to treatment period</u> are shown in Table 34 . As discussed in section 8.1 “Safety Review Approach’, the analysis of TEAEs includes all LEMS patients in the Safety Population without regard to the treatment arm as the double-blind period during which the patients were on placebo was very short in the two studies. Also, as discussed in section 8.3.2 ‘Categorization of Adverse events’, I performed regrouping of closely related adverse events, hence, the frequency of the TEAEs would differ from that of the applicant.

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Table 34 Treatment Emergent Adverse Events in Pivotal Studies Overall in Patients on Amifampridine Phosphate.

	Amifamiprdine Phosphate	
Treatment-emergent Common AEs	**LMS-002 N=53**	**LMS-003** N=13**
Paresthesia*	26 (49%)	
Upper respiratory tract infection	21 (40%)	
Back pain	9 (17%)	1 (8%)
Diarrhea	9 (17%)	
Muscle spasms	8 (15%)	
Asthenia	8 (15%)	
Abdominal pain	7 (13%)	
Elevated liver enzymes	7 (13%)	
Nausea	7 (13%)	
Constipation	6 (11%)	
Dizziness	6 (11%)	
Headache	6 (11%)	1 (8%)
Cataract	5 (9%)	
Dyspnea	5 (9%)	
Fall	5 (9%)	
Hypertension	5 (9%)	
Pain in extremity	5 (9%)	1 (8%)
Urinary tract infection	5 (9%)	
Bronchitis	4 (8%)	
Gastroesophageal reflux disease	4 (8%)	
Insomnia	4 (8%)	
Muscular weakness	4 (8%)	
Edema peripheral	4 (8%)	
Pyrexia	4 (8%)	
Viral infection	4 (8%)	
Blood creatine phosphokinase increased	3 (6%)	
Depression	3 (6%)	
Erythema	3 (6%)	
Hypercholesterolemia	3 (6%)	
Influenza	3 (6%)	
Lymphadenopathy	3 (6%)	

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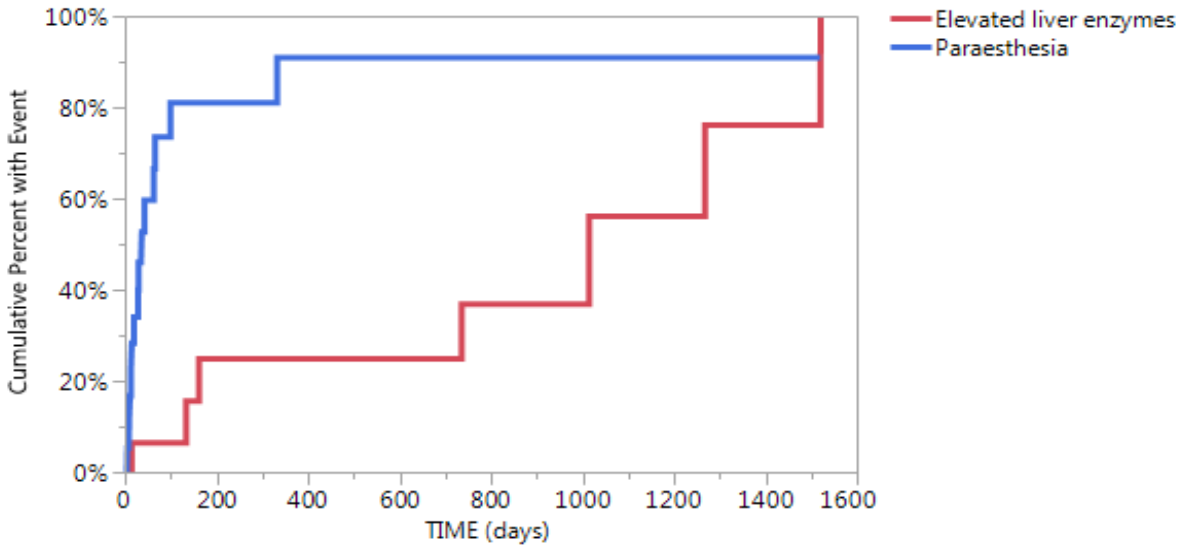
*This includes paresthesia, oral paresthesia and oral hypoesthesia
**Although the TEAEs from Study LMS-003 occurred in one patient each, these are reported in this Table for completeness of AEs observed in both studies.

Figure 10 shows time-to event plots to show the occurrence of AEs that have higher incidences. I have plotted a few AEs in each plot to unable a better separation between each AE for better visibility of time of onset during the study.

From these figures, it is evident that the onset of paresthesia is shortly after administration. All other events occurred throughout the study. In addition to the figures shown, I also looked at time to event plots of back pain, pain in the extremity, asthenia, muscle spasms and upper respiratory tract infections. These events occurred throughout the study.

Figure 10 Time-to-Major Adverse Events in Study LMS-002



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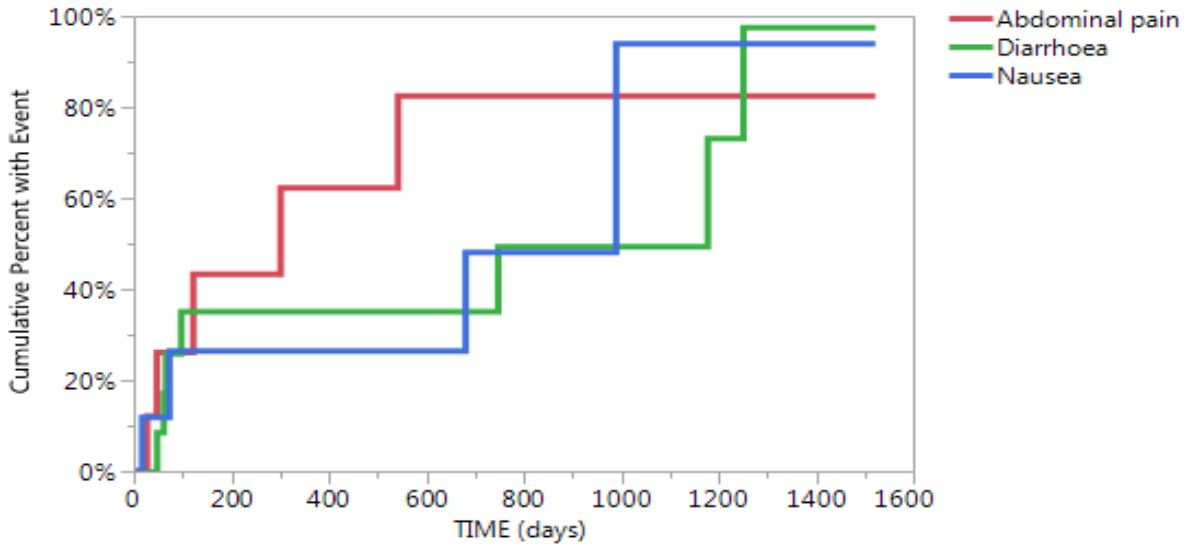

Study LMS-002 included 42 LEMS patients that were naïve to amifampridine phosphate and 11 that had prior experience with amifampridine phosphate. In Table 35, I summarize the TEAEs in naïve LEMS patients. As expected, paresthesia was a common TEAE in the naïve patients. Given the small number of patients (N=11) that had prior experience with amifampridine, a comparison of TEAEs in naïve and prior experienced patients would not be meaningful, hence TEAEs in only naïve patients have been reported in Table 35. In the literature as well, paresthesia is reported as a common AE. It is often reported around the mouth and extremities. The onset is shortly after administration and disappears in 15 minutes. A few patients also report multiple events of paresthesia during the study, although less frequent events of paresthesia were observed in later phases of the study, suggesting that patients likely become acclimated to the effects. The occurrence of paresthesia was not dose related. In 5 patients, the dose of amifampridine phosphate was reduced due to paresthesia.
Note: For paresthesia, the terms paresthesia, oral paresthesia, hypoesthesia and oral hypoesthesia have been regrouped in the Nervous System SOC.

Table 35 Treatment Emergent Adverse Events in Naïve Patients on Amifampridine Phosphate in Study LMS-002.

Treatment-emergent common AE	Amifampridine Phosphate Naïve N=42 N (%)
Paresthesia*	26 (62%)
Upper respiratory tract infection	14 (33%)
Abdominal pain	6 (14%)
Nausea	6 (14%)

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Diarrhea	6 (14%)
Headache	6 (14%)
Elevated liver enzymes	6 (14%)
Back pain	6 (14%)
Hypertension	5 (12%)
Muscle spasms	5 (12%)
Dizziness	4 (10%)
Asthenia	4 (10%)
Muscular weakness	4 (10%)
Pain in extremity	4 (10%)
Cataract	4 (10%)
Constipation	3 (7%)
Bronchitis	3 (7%)
Fall	3 (7%)
Lymphadenopathy	3 (7%)

*This includes paresthesia, oral paresthesia and oral hypoesthesia

The severity of paresthesia was mostly mild as shown in Table 36 and occurred mostly in the Run-In Phase of the Study LSM-002; however, three patients experienced it during the open label phase as well.

Table 36 Severity of Paresthesia in Naïve Patients

MedDRA Preferred Term	Mild (N=42) n (%)	Moderate (N=42) n (%)	Severe or Higher (N=42) n (%)
Paresthesia oral	16 (38.1%)	4 (9.6%)	0
Paresthesia	12 (28.6%)	6 (14.3%)	0

Clinical Pharmacology Studies:

Most Clinical Pharmacology studies were single dose studies, except for Study FIR-001 where subjects were given 4 doses. Similar regroupings as described under 8.3.2 'Categorization of Adverse events' were conducted for the analysis of incidences in healthy subjects. The applicant's analysis of incidences of paresthesia was complicated as the coding of AE term "Paresthesia oral" was distributed in two SOC-Nervous System Disorders and Gastrointestinal Disorders, based on the raw term describing the event. My regrouping pooled the terms paresthesia, oral paresthesia, hypoesthesia and oral hypoesthesia as "paresthesia" in the Nervous System SOC.

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The most common TEAE was paresthesia (paresthesia, hypoesthesia, paresthesia oral and hypoesthesia oral) occurring in majority of the subjects as shown in Table 37 . Other TEAEs were similar to those that occurred in LEMS patients. Since these are the same TEAEs that were observed in patients, they are likely treatment-related.

Table 37 Treatment-Emergent Adverse Events in Healthy Subjects

	Amifampridine N=158
AE Preferred Term	**N (%)**
Paresthesia	105 (66.5%)
Dizziness	37 (23.4%)
Headache	26 (16.5%)
Abdominal pain	23 (14.6%)
Hyperhidrosis	20 (12.7%)
Nausea	18 (11.4%)
Feeling of body temperature change	13 (8.2%)
Diarrhea	10 (6.3%)
Cold sweat	8 (5.1%)

8.4.6. Laboratory Findings

Laboratory assessments were conducted in Study LMS-002 and in the clinical pharmacology studies. As indicated under section 8.1 Review Approach, the database was searched for potentially significant outliers.

Serum Chemistry: I looked for subjects with abnormal serum chemistry parameters during the study that were normal at baseline and provide the number of subjects that were outside the reference range in Table 38. Amongst these abnormal values I also looked for subjects with potentially clinically significant outlier that based on criteria available in Attachment B of the Template for Safety Review. These are also reported in Table 38. Although there were isolated laboratory abnormalities, no trends were identified. A review of the outliers suggested that they were mostly single sporadic events that normalized at the subsequent assessment. In general, no clinical manifestations were observed. No follow-up assessments were made for any potentially significant outlier. Since laboratory assessments were conducted every 4 months in the open label extension, there was usually not a subsequent follow up of the observed laboratory outlier until 4 months later. Clinically significant outliers were reported as AEs.

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Table 38 Number of subjects with abnormal (outside of reference range) serum chemistry parameters that were normal at baseline and number of subjects that had potentially clinical significant (PCS) changes based on a given PCS criteria

Analyte	Potentially clinically significant Criteria (PCS)	Abnormal N	Subject no - # of events
Alanine Aminotransferase High	>3xULN (IU/L)	1 (0.02%)	(b) (6) -1 sporadic
Albumin Low	<2.5 (g/dL)	0	0
Alkaline Phosphatase High	>400 (IU/L)	0	0
Aspartate Aminotransferase High	>3xULN (IU/L)	1 (0.02%)	(b) (6) -1 sporadic
Bilirubin High	>2 (mg/dL)	0	0
Blood Urea Nitrogen High	>30 (mg/dL)	1 (0.02%)	(b) (6) -2 sporadic (b) (6) -1 sporadic
Calcium High	>12 (mg/dL)		0
Calcium Low	<7 (mg/dL)		0
Chloride Low	<90 (mEq/L)	1 (0.02%)	(b) (6) 1 sporadic
Chloride High	>112 (mEq/L)	2 (0.04%)	(b) (6) 1 sporadic (b) (6) 1 sporadic
Carbon dioxide High	>34 (mEq/L)	1	0
Carbon dioxide Low	<17mEq/L	3 (0.06%)	(b) (6) 1 sporadic (b) (6) 1 sporadic (b) (6) 1 sporadic
Cholesterol	>300 (mg/dL)	10	0
Creatine Kinase	>3xULN (IU/L)	8	(b) (6) 1 sporadic
Creatinine High	>2 (mg/dL)	2	0
Gamma Glutamyl Transferase High	>3xULN (IU/L)	1 (0.02%)	(b) (6) 1 sporadic
Glucose High	>250 (mg/dL)	16	0
Glucose Low	<50 (mg/dL)	11	0
Lactate Dehydrogenase High	>3xULN (IU/L)	12	0
Phosphate High	>5.0 (mg/dL)	1 (0.02%)	(b) (6) 1 sporadic
Phosphate Low	<2.0 (mg/dL)	2	0
Potassium High	>5.5 (mEq/L)	2 (0.04%)	(b) (6) 1 sporadic (b) (6) 1 sporadic
Potassium Low	<3.0 (mEq/L)	4	0
Sodium High	>150 (mEq/L)	3	0
Sodium Low	<130 (mEq/L)	1 (0.02%)	(b) (6) 1 sporadic

Elevated Liver enzymes: Elevated liver enzymes as an AE was observed in 13% of the patients in Study LMS-002 during the extension phase of the study. There were no Hy's Law cases in the

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safety database of amifampridine phosphate. Several subjects had an increase in ALT, AST and GGT above the ULN without an increase in bilirubin above the ULN.

There was one patient ([redacted] (b) (6)) who had an increase in ALT, AST and GGT that were >3XULN (188, 157 and 142 IU/L respectively) at only one instance in the open label extension phase (Day 1015) of the study at a dose of 50 mg/day. Only GGT was reported for the subsequent visit that became normal. This was the last assessment for this patient. Elevated liver enzymes were reported as an AE for this patient of moderate intensity that recovered. This patient was on several concomitant medications; hence the attribution of the increase in liver function test to amifampridine phosphate remains unclear. The dose of amifampridine phosphate in this patient remained unchanged.

A second subject ([redacted] (b) (6)), a 24-year-old female on 80 mg/day amifampridine phosphate also had an increase in asymptomatic increase in ALT of >2.5XULN on one instance (Day 736 post enrollment) in the open label extension that became normal at the next visit. The bilirubin was normal. Relevant medical history and concomitant medications were not reported. The dose of study drug was reduced and the event resolved. (The applicant lists this patient as having a >3xULN increase in ALT).

The applicant also reports that Patient [redacted] (b) (6), a 55-year-old man on 80 mg/day amifampridine phosphate had a SAE of high ALT of 169 IU/L at Day 1520 post enrollment. Other reported labs: AST 68 U/L, bilirubin 0.77 mg/dL, and GGTP 72 U/L. The patient was reported to have a medical history of fatty liver. The event was assessed as mild and drug was titrated down to 0 mg. According to the narrative, the event resolved in 15 days. However, the patient was discontinued from open label extension phase of the study.

One subject in the clinical pharmacology study [redacted] (b) (6)) had a 4.6xULN increase in ALT and 3.5xULN increase in AST within 24 hours after the first 20 mg of 3,4 DAP base administration without any clinical symptoms. This subject was discontinued from the study. No other laboratory abnormality was observed. The increase in ALT and AST appeared reversible and improved a month later. Hepatic virology tests remained negative. No medical history or information on concomitant medications is provided for this subject. This subjects ALT and AST are shown in below. The causality to 3,4 DAP base cannot be ruled out due to the fact that this occurred within 24 hours of dosing.

Event time in relation to last dose	AST	ALT
24 hours	3.5XULN	4.6xULN
48 hours	2.1xULN	3.8xULN
1 month	1.5xULN	2.7xULN

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Note: At screening, the subject had normal ALT and AST, actual laboratory values at screening are provided. Actual values of AST and ALT at the time of severe AE and its follow up are not provided in the report

No other clinically significant increases in serum liver enzymes were observed in these studies. Overall, the increase in liver enzymes does not appear dose related, given that the DAPSEL subject had an increase in liver enzymes at 20 mg/day.

Other Chemistry Parameters: Sporadic increases in some of the other chemistry parameters were observed in various phases of the study, which did not have a trend and became normal at subsequent visits. I reviewed individual cases and none were found to be of clinical significance.

None of the clinical pharmacology studies had clinically significant increases in chemistry parameters.

Hematology Parameters:

I looked for subjects with abnormal hematology parameters during the study that were normal at baseline. I then looked for treatment related trends and significant outliers within these subjects with abnormal values. A discussion of the outliers is summarized below:

Table 39 Number of subjects with abnormal (outside of reference range) hematology parameters that were normal at baseline

Analyte	Potentially clinically significant Criteria (PCS)	Subject no - # of events
Eosinophil (THOU/MCL) high	>1	(b) (6) 1 sporadic
Hemoglobin (g/dL) low	<8	(b) (6) 1 sporadic
Hematocrit (%) low	<23	(b) (6) 1 sporadic
Monocyte high	≥1.1	
Lymphocytes (THOU/MCL) (Low)	<0.8	(b) (6) -1 sporadic
Neutrophils/Total Cells (THOU/MCL) low	<1.5	(b) (6) 1 sporadic, always low-1 event
Platelets (PER CUMM) (Low)	<75000	(b) (6) 1 sporadic

Eosinophil: A few patients had minor increases in eosinophils that were not clinically significant and that did not result in any clinical manifestations. Only one patient ((b) (6)) with a

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history of autoimmune diseases such as autoimmune thyroiditis, vitiligo and cancer had eosinophil value >1 THOU/MCL (reference range 0.05-0.55 THOU/MCL) that was normal at baseline. A high eosinophil is expected in such patients.
Hemoglobin/Hematocrit: Most of the patients had small decreases in the hemoglobin (Hb)/Hematocrit that are not clinically significant. Patient # (b) (6) had a value of 12.4 g/dL at baseline that decreased to 7.5 g/dL in the Run-in phase. During the Run-in through the open-label extension phase the Hb values remained low, but gradually increased from between 7.5 to 9.7. Anemia was reported as a TEAE in the Run-in phase for this patient and was also recorded in the patient's medical history. This same patient also had a low hematocrit that was in the range of 23.4-27.3% (reference 35-46%) during the study. No other patient in the safety population had values that showed decreases in Hb or hematocrit to the same extent.
Lymphocytes: One patient had decrease in lymphocyte count ≤0.5 THOU/MCL (reference range 0.85-4.1 THOU/MCL) (# (b) (6)). A subcutaneous abscess and sinusitis were reported as TEAEs for this patient. Another patient (# (b) (6)) with a medical history of peptic ulcer, peripheral edema and thrombocytopenia showed a sporadic decrease in lymphocyte count to 0.48 THOU/MCL. This patient had an increase in peripheral edema as a TEAE reported during the study. One patient with a baseline of 0.83 THOU/MCL had a single event of a high lymphocyte count of 4.94. This patient had AEs of viral infection, calculus urinary, hydronephrosis and pyelonephritis acute. In general, there appears to be no treatment related trend in abnormal lymphotocytes.
Platelets: One patient (# (b) (6) had a decrease in platelet of <75000 PER CUMM. This patient also had decrease in lymphocytes and hematocrit. A subcutaneous abscess and sinusitis were reported as TEAEs for this patient. A few other patients had abnormal platelets, but these patients were on multiple drugs and changes were sporadic and normalized at subsequent visits.
Others: No clinically significant changes were observed in basophils, neutrophils and leukocytes.

None of the clinical pharmacology studies had clinically significant increases in hematology parameters.

8.4.7. Vital Signs

I analyzed the vital signs including weight, body mass index, temperature, heart rate, diastolic and systolic blood pressure. Changes from baseline were not clinically significant for any vital sign.

8.4.8. Electrocardiograms (ECGs)

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No changes or clinically significant trends were seen for QT-interval, QTcF-interval, QTcB-interval, PR-interval, QRS-interval and heart rate. I looked for outliers. No clinically significant outliers were found in any study.

8.4.9. QT

The application included a Thorough QT Study which was designed in 2 parts. Part 1 was a randomized, double-blind, single-dose, escalation study, 6 subjects received single oral doses of 30 mg, 60 mg, 70 mg, and 80 mg amifampridine for a total exposure of 240 mg amifampridine per subject. Part 2 was a double-blind (except for moxifloxacin), randomized, single-site, 4-arm crossover design, 51 subjects received 30- mg amifampridine, 60-mg amifampridine, placebo, and moxifloxacin 400 mg.

Based on the review of the Thorough QT Study by the FDA Interdisciplinary Review Team (IRT), at the doses (30 mg and 60 mg) and exposures achieved in this study, there was no significant QTc prolongation effect of amifampridine phosphate detected in this TQT study as shown in Table 40. The largest upper bounds of the 2-sided 90% CI for the mean differences between amifampridine 30 mg and placebo, and between amifampridine phosphate 60 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

Table 40 The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for for Amifampridine (dosed of 30 mg and 60 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis: IRT)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
30-mg Amifampridine	3	3.6	(0.8, 6.4)
60-mg Amifampridine	4	5.6	(2.9, 8.4)
400 mg Moxifloxacin	4	10.6	(7.9, 13.4)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 6.9 ms.
Source: IRT Review

The supratherapeutic single 60 mg dose produces mean amifampridine phosphate C_{max} approximately 2-fold the mean maximum therapeutic C_{max} (i.e., at steady state with the proposed highest clinical dosing regimen, 20 mg q.i.d., in slow acetylator phenotype). Renal impairment has been reported to increase amifampridine phosphate exposure. There was less than a 1.5-fold increase in C_{max} of amifampridine phosphate in subjects with renal impairment. Administration of amifampridine phosphate with food as conducted in this study significantly decreased amifampridine phosphate C_{max} (~ by 40%). (b) (4) Overall, the exposure with the supratherapeutic single 60 mg dose covers the

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expected high clinical exposure scenario for amifampridine phosphate. However, the study was conducted in only slow acetylators in order to maximize amifampridine exposure. In this case, exposures of metabolite 3-N-acetyl-amifampridine may not be covered (clear information of 3-N-acetyl-amifampridine in fast acetylators (and especially in renal impairment patients) is not available. A statistically significant positive relationship between ΔΔQTcF and amifampridine metabolite (3-N-acetyl-amifampridine) concentrations was observed (slope = 0.0193 with 95% CI (0.0125, 0.0261). Although the predicted placebo-corrected change in QTcF is less than 10 ms at the geometric mean C_{maxs} of the doses studied in this study, the drug effect on QTc interval in fast acetylators with renal impairment cannot be reliably predicted (excerpted from FDA IRT review).

8.4.10. Immunogenicity

Not applicable

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Seizures

Based on observations from structurally related compounds, such as 4-aminopyridine, and the animal toxicology studies that identified seizures as potential risk, the amifampridine phosphate development program identified seizures as an AE of interest. Tissue distribution studies in rats and dogs indicated that amifampridine phosphate has low central nervous system penetration.

No seizures were reported in the clinical development program for amifampridine phosphate (studies LMS-002, LMS-002 extension, LMS-003 and the clinical pharmacology studies).

The applicant reported five patients that experienced seizures from the LEMS-Registry and Expanded Access Study EAP-001. The narratives of these cases are discussed below.

Case 1 (EAP-001-[redacted] (b) (6))
A 87-year-old white female was hospitalized after experiencing seizure episodes. The patient had been exposed to amifampridine phosphate for 1 year and 3 months prior to the recurrent seizure episodes. The most recent dose at the time of the event was 50 mg/day. Two months prior to the event of seizure the patient had been treated for aspiration pneumonia and sepsis and was still being treated with cefipime and ampicillin/sulbactam. The patient was hospitalized and was found to have pneumonia and aurinary tract infection at the time of the seizure. The patient was treated with levetiracetam. It is not reported if any changes were made to the

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amifampridine phosphate. The seizure episodes are confounded by the concurrent infection and the use of cefipime and ampicillin that may lower seizure threshold.

Case 2 (EAP-001 (b) (6)
A 75-year-old white female experienced tonic-clonic seizure-like symptoms after about three months of exposure to amifampridine phosphate. The dose at the time of the event was 50 mg/day. Patient was hospitalized after having syncopal episodes described as head rolling back to the right side and eyes rolling back in her head with tonic-clonic movements of the upper extremities. The patient was felt to have tonic-clonic seizures related to use of amifampridine phosphate. No seizures were observed in the hospital. Anti-epileptic drugs were not started and MRI was unremarkable. It is not reported if any changes were made to the amifampridine phosphate. Concomitant medications include levofloxacin, azathioprine and pyridostigmine that can lower seizure threshold, and therefore, confound the causality to amifampridine phosphate.

Case 3 (EAP-001- (b) (6)
A 77-year-old white female experienced seizure-like symptoms after about 3 months of exposure to amifampridine phosphate. The most recent dose taken a day before the event was 70 mg/day. The patient was initiated on treatment with 30 mg/day. It is unclear when the dose was increased to 70mg/day in relation to the seizure episode. The event was described as "shaking, frothing and eyeball rolling backwards." A CT of the head revealed an old lacunar left anterior internal capsule lacunar infarct. Continuous EEG monitoring showed frequent right temporal flowing with no epileptiform discharge. Levetiracetam was initiated. The seizure was attributed to the old stroke and the amifampridine phosphate; however, the description of the infarct sounds like an incidental finding on CT. The narrative reports a medical history of tonic-clonic seizure. Given, the medical history of the patient, the causality to amifampridine phosphate is unclear.

The 120-day safety update reports a 2nd episode of seizure after 11 months of exposure to amifampridine phosphate in this patient. The patient was on 60 mg/day amifampridine phosphate at the time of this event. At that time, the patient was also on amoxicillin clavulante for a urinary tract infection which can also lower seizure threshold. The CT compared to the previous one showed no significant change in the brain. When compared with ECG done after the 1st seizure, premature atrial complexes were present. An EEG was also performed. EEG result was normal with no focal, diffuse or generalized abnormalities.

Case 4 (EU LEMS Registry (b) (6)
A 71-year-old white female was hospitalized for a seizure after about 54 months of exposure to amifampridine (as the free base) at 70 mg/day. The patient had a prior history of epilepsy. Electroencephalogram and Angio-TDM were reported as normal. Treatment for the event

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included clobazam. Dosing with amifampridine phosphate was reduced to 60 mg/day due to the event and no sequela was noted. Patient was discharged in a day.

Case 5 (EAP-001- (b) (6)
This event was reported in the 120-day safety update. A 69-year-old female with no history of seizure, experienced a severe seizure approximately 2 years and 5 months after beginning treatment with amifampridine phosphate for LEMS. The subject began amifampridine phosphate treatment with a starting dose of 40 mg. The most recent dose before the seizure was 80 mg. While in the emergency department, the subject experienced poor respiration, had another seizure, and went into respiratory failure. Following temporary intubation, the subject's conditions improved. The subject was found to have aspiration pneumonia and was treated with IV antibiotics. Amifampridine phosphate was discontinued for 4 days. This event was a new-onset seizure with no clear provocative cause.

Overall, a clear causal relationship of seizures to amifampridine phosphate cannot be established based on the all the cases of seizures. The first 4 cases from the registry were confounded by comorbid medical conditions, concomitant medications or prior history of seizures. The case of seizure provided in the 120-day safety update has no provocative cause for seizure and may possibly be drug-related; however, there was a long latency period after initiating treatment with amifampridine phosphate. There was no clear dose-response in the registry reports (seizures were reported at doses ≥50 mg/day); however, in the literature, occurrence of seizures was reported to be dose related. There was not a clear temporal relationship between seizures and the initiation of amifampridine phosphate. Nevertheless, since a seizures was an identified risk in a structurally similar compound, dalfampridine, and there are nonclinical findings that suggest a risk for seizures, the risk of seizures should be considered as a warning in the product label, if approved.

8.5.2. Cardiac Disorders

There is no non-clinical evidence of cardiac toxicity with amifampridine phosphate. In addition, the Thorough QTc Study was also negative. (b) (4) ECG was a pre-specified safety assessment in Study LMS-002 and the clinical pharmacology studies to capture any cardiac events. No clinically significant findings on ECG were observed.

The applicant summarized all the cardiac related disorders in the TEAEs for the assessment of cardiac disorders in the development program. It grouped the cardiac related disorders in categories such as palpitations, arrhythmias (includes atrial fibrillation, tachycardia, sinus

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bradycardia, sick sinus syndrome, ventricular extrasystoles, cardiac arrest), heart disease (includes heart failure), myocardial disease (includes myocardial ischemia, stress cardiomyopathy, acute myocardial infarction), cardiac clinical finding (includes cyanosis), disorders of cardiovascular system (includes presyncope), heart valve disorder (includes mitral valve prolapse), structural disorders of the heart (includes acute coronary syndrome). This analysis of cardiac disorders is limited due to the lack of any control in the analysis.

For the review of these events, I searched for cardiac related AEs in the applicant's development program (LMS-002, LMS-003, Expanded Access Study (EAP-001) and EU LEMS Registry to verify the number of cardiac-related events. I reviewed all the narratives associated with cardiac-related events and discuss the findings in this section.

Cardiac-Related Deaths
There were 4 cardiac-related deaths reported in the application from the EU LEMS Registry and Study EAP-001. These have been described in in Section 8.4.1. These cases either had confounding risk factors such as lung cancer and metastases or lacked detail to assess the causal relationship to amifampridine phosphate. One additional case was reported in the 120-day safety update of the application (see section 8.41. Deaths).

Cardiac-related SAEs:
There were 4 cases of SAEs of cardiac arrest/cardiac failure in the application from the EU LEMS Registry and Study EAP-001 (see section 8.41. Deaths). Two of these resulted in death and two resolved. There was one patient that was reported with stress cardiomyopathy that resolved and one with acute coronary syndrome that died. These cases either had confounding risk factors or lacked detail to assess the causal relationship to amifampridine phosphate.

Palpitations:
The applicant notes palpitations as a "probably" drug-related AE. The palpitation events and the causality assessment are described in Table 41. Most cases of palpitation were mild, not dose dependent, did not require dose reduction, and resolved within 1-15 days. Overall, the causal relationship of palpitations to amifampridine phosphate is unclear based on the cases described in Table 41. Palpitations are a common and non-specific symptom.

Table 41 Reports of Palpitations in the LEMS development program

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Study # Patient ID	Age/Gender	AE onset day	Dose at AE onset	Dose reduction at AE onset	Event Severity and resolution	Reviewer Comments
LMS-002 (b) (6)	66 years/F	10 days post enrollment	25 mg/day	none	Moderate; resolved in 5 days	Medical history includes coronary artery disease, hypertension, myocardial infarction. Subject on confounding concomitant medications (synthroid, lasix, advair, albuterol sulfate, metoprolol, aspirin, acetaminophen/oxycodone), no other information on concomitant medications, no correlation to vitals or ECG
LMS-002 (b) (6)	49 years/F	827 days post enrollment	80 mg/day	Dose reduced to 35 mg/day	Moderate; resolved in 1 day	Medical history includes asymptomatic bradycardia, no correlation to vitals or ECG
FIR-001 (b) (6)	26 years/M	4 days post treatment	20 mg SD	none	Mild, resolved	Medical history includes heart palpitations, no correlation to vitals
QTC-002 (b) (6)	33 years/F	1 day post treatment	60 mg SD	none	Mild, resolved in 15 minutes	Medical history includes anxiety, no correlation to vitals or ECG

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REN-002 (b) (6)	60 years/M	14 days post treatment	10 mg SD	none	Mild, resolved	Confounding medical history includes aneurysm of thoracic aorta, arterial hypertension, atrial fibrillation, chronic renal disease, diabetes mellitus type II, dyslipidemia, history of stroke, ischemic heart disease, left ventricular failure, and confounding concomitant medication (allopurinol, amlodipine, atorvastatin, bisoprolol, bromazepam, dabigatran, digoxin, furosemide, insulin glargine, ramipril, trandopril and urapidil), no other information on concomitant medications, no correlation to vitals
EAP-001 (b) (6)	22 years/F	3 months post treatment	75 mg/day	none	resolved in 5 days	Inadequate information
EAP-001 (b) (6)	67 years/M	7 days post treatment	40 mg/day	none	Resolved in 15 days	Inadequate information

Cardiac Arrhythmias:

(b) (4) I reviewed all events of arrhythmias and their narratives. Table 42 summarizes the events based on the information included in the narratives and includes my comments on the case.

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Table 42 Incidences of Cardiac Arrhythmias in the LEMS Development Program

Study # Patient ID	Age (yrs) M/F	Preferred Term or Event	AE onset day	Dose at AE onset	Dose reduction at AE onset	Event Severity and resolution	Reviewer Comments
LMS-002 (b) (6)	49 y F	Atrial fibrillation and worsening or atrial fibrillation	78 days and 827 days post enrollment	50 mg/d	none	Mild; not resolved	An initial event of atrial fibrillation was reported at 78 days post-enrollment that resolved on the same day. There is no description of this event. A second event of "worsening of atrial fibrilliation" was reported at 827 days post-enrollment. Medical history includes asymptomatic bradycardia, anxiety, hyperlipidemia. ECG from the second event was "abnormal interpretation but not clinically significant". The ECG findings were as follows: heart rate 55 bpm, PR 152msec, RR 1090 msec, QRS 74 msec and QT 474 msec. Insufficient information was provided to assess causality.
LMS-002 (b) (6)	75y F	Tachycardia	2 days post enrollment	30 mg/d	none	Mild; not resolved	The patient reported tachycardia 2 days post-enrollment. Medical history includes hypertension, diabetes, hyperlipidemia. Patient was on multiple concomitant medications including amlodipine besylate, lisinopril glipizide, metformin, pyridostigmine bromide. In a separate SAE report at 5 days post enrollment the patient experienced a SAE of respiratory failure and was diagnosed with pulmonary embolism due to deep vein thrombosis. ECG revealed sinus tachycardia with poor R-wave progression. The patient was withdrawn during the Run-in phase of the study.
EAP-001 (b) (6)	22y F	Tachycardia	593 days post enrollment	75 mg/d	NA	NA	Insufficient information was provided to assess causality.
LMS-002 (b) (6)	65y F	Sinus bradycardia	695 days	50 mg/d	none	resolved	Patient was hospitalized with a SAE of Sinus bradycardia, 695 days post-enrollment. Patient experienced a pre-

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			post enrollment				syncopal episode. The patient had been hospitalized for gastroenteritis and syncope 2 weeks preceding the event, and had prior history of general weakness and recurrent syncope. ECG on admission did not reveal any signs of cardiac arrhythmia or myocardial ischemia and troponin level was insignificantly elevated. A transient loss of consciousness was observed in the patient during hospitalization which was recorded by Holter ECG as an 8 second pause. A pacemaker was implanted and patient was discharged. Medical history includes hypertension treated with amlodipine and hyperlipidemia. The patient is also noted to have moderate renal impairment on labs.
LMS-002 (b) (6)	88y F	Sick Sinus Syndrome	250 days post enrollment	75 mg/d	Interrupted for 2 days at AE onset	Moderate, recovered	No description of the event is provided. Onset 250 days after enrollment; resolved in two days. Insufficient information on the event.
EAP-001 (b) (6)	74y M	Arrhythmia	Day 136	10 mg	NA	Recovered	No description of the event. Patient had a history of atrial fibrillation, hypertension, hyperlipidemia, mild diastolic dysfunction, COPD, bladder cancer and sleep problems. Patient was on multiple concomitant medications. Insufficient information on the event.
EU-Registry (b) (6)	72y M	Ventricular extrasystoles	5 y on drug	80 mg	none	Mild, resolved	Ventricular ectopic beats (bigeminy) identified on ECG. Treated successfully with flecainide acetate. No change to amifampridine dose. Medical history included myocardial infarction, aortic valve repair.
EAP-001- (b) (6) (120-day update)	53y F	Refractory paroxysmal atrial fibrillation	2 y on drug	43 mg/d	NA	Not serious, resolved	No description of the event is provided. Medical history included bradycardia, heart palpitations, and intermittent atrial fibrillation.

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Others:

The applicant lists other cardiac diseases as such congestive heart failure, cardiac insufficiency, myocardial ischemia, stress cardiomyopathy, cyanosis, presyncope, mitral valve prolapse. I reviewed the narratives of all these cases. Patients with these cases had either had confounding risk factors or lacked detail to assess causality to amifampridine phosphate.

The majority of the cardiac cases lacked sufficient information to determine causality. The remaining cases were confounded by prior history of cardiac disease, cardiac risk factors, comorbid medical conditions, or concomitant medications. Although the contribution of amifampridine phosphate to the events cannot be completely ruled out, it is not possible to assess causality of these events. (b) (4)

8.6. Safety Analyses by Demographic Subgroups

Age

Overall in the Studies LMS-002 and LMS-003 and LMS-002EXT there were 16 patients of ages ≥65 years and 47 patients of ages <65 years. The number and percentage of patients who experienced at least 1 TEAE was 14 (88%) for patients ≥65 years and 38 (81%) for patients <65 years. The total number of patients in ≥65 years group was much less compared to the patients <65 years to derive any interpretable differences between age groups.

Sex

Overall in the Studies LMS-002 and LMS-003 and LMS-002EXT there were 23 males and 40 females. The number and percentage of patients who experienced at least 1 TEAE was 16 (70%) for males and 35 (88%) for females. The total number of patients in each gender was not comparable to derive any interpretable differences between gender groups.

Race

Overall in the Studies LMS-002 and LMS-003 and LMS-002EXT there were 57 White patients and 4 patients of other race. No interpretable safety comparisons related to race can be made.

8.7. Specific Safety Studies/Clinical Trials

No specific clinical safety studies were performed in the amifampridine phosphate development program.

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8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

In 50-60% of the patients with LEMS cancer is present when either weakness begins or is found later. LEMS is associated with small cell lung carcinoma (SCLC), non-SCLC, lymphosarcoma, malignant thymoma, or carcinoma of the breast, stomach, colon, prostate, bladder, kidney, or gallbladder. Therefore, drug-related tumor development would be difficult to detect in this patient population.

8.8.2. Human Reproduction and Pregnancy

No adequate well controlled studies have been conducted in pregnant women. No pregnancies were reported in the studies.

It is not known whether amifampridine is excreted in human breast milk.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose: There has been one report[2] and one case in the EU LEMS Registry regarding overdose with amifampridine that are summarized below.

- It was suspected that an overdose led to generalized convulsions and sudden unexplained cardiac arrest in a 65-year-old subject with LEMS, idiopathic thrombocytopenic purpura, and non-insulin dependent diabetes mellitus. The patient was admitted to the hospital due to general weakness, paresthesia, nausea, vomiting and palpitations. The subject subsequently experienced generalized convulsions that resolved with IV clonazepam therapy and paroxysmal supraventricular tachycardia that resolved with digoxin. Four days after admission, the subject experienced a sudden, unexplained cardiac arrest and was successfully resuscitated. It was then discovered that 7 days prior to admission the subject was incorrectly given more than 3-times the maximum recommended total daily dose of amifampridine; she was given 60 mg 6 times per day (360 mg/day) rather than the intended 10 mg 6 times per day (60 mg/day) due to a typing error. The subject made a full recovery after withdrawal of amifampridine for 5 days and was later discharged.

[2] Boerma CE, Rommes JH, van Leeuwen RB, Bakker J. Cardiac arrest following an iatrogenic 3,4-diaminopyridine intoxication in a patient with Lambert-Eaton myasthenic syndrome. J Toxicol Clin Toxicol 1995;33(3):249-251.

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The authors concluded that amifampridine overdose could be treated by prevention of absorption with gastric lavage and activated charcoal, and by treating the patient's symptoms (antiemetics, anticonvulsive therapy). In severe overdose cases, the authors recommend forced diuresis and hemoperfusion.

- The narrative on the patient from the LEMS registry was noted to take more than 9 tablets of Fridapse that was thought to be the reason for the worsening on ataxia. The actual dose taken by the patient is not provided.

Abuse Potential: The applicant also conducted a human abuse potential study, which was evaluated by the Controlled Substance Staff (CSS). They concluded that amifampridine phosphate does not have any abuse potential.

Withdrawal effects: In Study LMS-003, patients on amifampridine phosphate underwent an immediate withdrawal of drug in one arm. Patients deteriorated in the LEMS symptoms. The evaluation period was 4 days. There was no increase in adverse events after abrupt withdrawal of the drug, other than a return of LEMS Symptoms. A higher incidence of adverse events was observed in the placebo arm compared to amifamprdine phosphate arm.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Safety findings from the EU-LEMS Registry were included in the review of deaths, SAE and AEs of interest in this review in the relevant sections of the review.

8.9.2. Expectations on Safety in the Postmarket Setting

Additional information regarding amifampridine phosphate known clinical safety issues will be obtained and new safety issues likely identified as there are more patients exposed for increasing durations of treatment.

If it is approved, amifampridine phosphate may be administered at higher doses than the clinical studies as the drug is titrated to effect. We anticipate use of amifampridine phosphate in congenital myasthenia gravis.

8.9.3. Additional Safety Issues From Other Disciplines

None

8.10. Integrated Assessment of Safety

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The most commonly observed adverse event with amifampridine phosphate was paresthesia. The paresthesia was more common in treatment naïve patients and incidences of paresthesia were largely reduced in 2 year-open label extension phase of the study. The other common adverse events include gastrointestinal disorders: nausea, diarrhea, abdominal pain. TEAEs mostly did not require dose reduction or withdrawal.

Five cases of seizures were reported in the EU Registry and the US Expanded access program. Causality to amifampridine phosphate was not very clear in these cases. However, given the structural similarity to dalfampridine, which has a warning for seizures, attribution of amifampridine phosphate to seizures cannot be ruled out.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Please see edits proposed for labeling in separate labeling review.

11. Risk Evaluation and Mitigation Strategies (REMS)

At the time of this review completion, no REMS have been determined for this application.

12. Postmarketing Requirements and Commitments

A global pregnancy registry is being considered for this application as follows.

Establish a worldwide Pregnancy Surveillance Program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to

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amifampridine during pregnancy. Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g. telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis and yearly reporting.

13. Appendices

13.1. References

- Sanders DB. Lambert-Eaton Myasthenic Syndrome: diagnosis and treatment. Ann N Y Acad Sci 2003; 998:500-508.
- Titulaer Maarten. Lambert-Eaton Myasthenic Syndrome: from clinical characteristics to therapeutics strategies 2011; 10:1098-107
- Wirtz, P.W. The epidemiology of Lambert-Eaton Myasthenic Syndrome in Netherlands 2004; Neurology July 2
- O'Neill JH, Murray NM, Newsom-Davis J. The Lambert-Eaton Myasthenic Syndrome. A review of 50 cases. Brain 1988; 111:577–596.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): LMS-002 and LMS-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 23		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): not stated		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

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Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 23		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VENEETA TANDON
11/28/2018

JUNSHAN QIU
11/28/2018

KUN JIN
11/28/2018
I concur with the statistical review.

HSIEN MING J HUNG
11/28/2018

TERESA J BURACCHIO
11/28/2018