CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Amifampridine Phosphate in Patients with MuSK Antibody Positive Myasthenia Gravis, and a Sample of AChR Antibody Positive Myasthenia Gravis Patients
Protocol Number:	MSK-002
Investigational Product:	Amifampridine phosphate (3,4-diaminopyridine phosphate)
IND/EUDRACT Number:	106263 / 2015-03127-62
Indication:	Musk Antibody Positive Myasthenia Gravis
External Support:	Catalyst Pharmaceuticals, Inc.
Development Phase:	Phase 3
Medical Officer:	Gary Ingenito, MD, PhD
Study Design:	Double-blind, Placebo-controlled, Randomized, Parallel Group, Withdrawal
Dose:	30-80 mg total daily dose or placebo equivalent
Patient Population:	Patients with MuSK antibody positive Myasthenia Gravis and a sample of patients with AChR antibody positive Myasthenia Gravis
Date of Protocol:	June 27, 2017

PROCEDURES IN CASE OF AN EMERGENCY

Emergency Contact Information

Role in Study	Name	Contact Information
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2 SYNOPSIS

TITLE OF STUDY:
A Randomized, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of Amifampridine Phosphate in Patients with MuSK Antibody Positive Myasthenia Gravis, and a Sample of AChR Antibody Positive Myasthenia Gravis Patients

PROTOCOL NUMBER:
MSK-002

STUDY SITE:
Up to 20 sites in USA, Europe, and Canada

PHASE OF DEVELOPMENT:
Phase 3

STUDY RATIONALE:
The purpose of this study is to evaluate the safety, tolerability, and efficacy of amifampridine phosphate in patients with MuSK antibody positive myasthenia gravis (MuSK-MG), and a sample of AChR antibody positive Myasthenia Gravis (AChR-MG) patients.

OBJECTIVES:

Primary

- To characterize the overall safety and tolerability of amifampridine phosphate compared with placebo in patients with MuSK-MG; and
- To assess the clinical efficacy of amifampridine phosphate compared with placebo in patients with MuSK-MG based on change in Myasthenia Gravis Activities of Daily Living Score (MG-ADL).

Secondary

- To assess the clinical efficacy of amifampridine phosphate compared with placebo using the Quantitative Myasthenia Gravis (QMG) score.
- To assess the safety and efficacy of amifampridine phosphate compared with placebo in a sample of patients with AChR-MG (N equal to 10).

STUDY DESIGN AND PLAN:
This randomized (1:1), double-blind, placebo-controlled, parallel group, outpatient study is designed to evaluate the safety, tolerability and efficacy of amifampridine phosphate in patients diagnosed with MuSK-MG. In addition, a sample of AChR-MG patients (N equal to 10) will be assessed for efficacy and safety of amifampridine with the same study design. If it is determined that 18 or more of the first 20 screened AChR-MG patients fail to meet inclusion criteria, additional screening for AChR-MG patients will be terminated. If the AChR-MG screening failure rate is lower, an additional 20 patients will be screened; overall, up to 40 AChR-MG patients may be screened to try and enroll 10 in the study. The study is planned to include approximately 60 male and female MuSK-MG patients and 10 AChR-MG patients. The planned duration of

participation for each patient is at least 38 days, excluding the screening period, which can last up to 14 days. In addition to investigational product (amifampridine phosphate 10 mg tablets or matching placebo tablets), patients will continue to receive stable dose of pyridostigmine and/or corticosteroid therapy, but no new therapies and no change in dose is permitted during the study.

All patients who sign an informed consent will be screened for eligibility to participate in the study, and those successfully completing screening will have procedures/assessments (see Table 1) completed during Run-in, until an optimized stable dose and frequency of amifampridine phosphate is established. At the end of 7 days on a stable dose, the patient must show ≥2-point improvement in MG-ADL score to be randomized. On Day 0 (randomization), procedures/ assessments (see Table 1) will be conducted to confirm eligibility for randomization, including a negative urine pregnancy test.

Open-label Run-in

Amifampridine dose will be titrated upward every 3 to 4 days, starting at 10 or 15 mg/day, at the discretion of the Investigator. Patients will either visit or have telephone/video contact with the site for each dose titration and at least one in-person site evaluation at Week 3 of the run-in period. When the Investigator determines that the patient has reached the maximal tolerable and efficacious dose, the patient should demonstrate they can remain on a stable dose and frequency for at least an additional 7 days. The Open-label Run-in period may be extended if additional time is needed for dose titration. At the end of this period, patients must show a ≥2-point improvement in MG-ADL from start of Run-in, to be eligible for randomization (Day 0).

Period 1 (Days 1-10) (+1 day)

Patients who have successfully completed the open-label run-in and continue to meet all inclusion/exclusion criteria will be randomized (1:1 ratio) on Day 0 to receive either amifampridine tablets (10 mg as amifampridine phosphate) or placebo tablets for 10 days, beginning on Day 0 after assessments have been performed on open-label medication. Test medication will be dispensed by the site pharmacist, according to the randomization schedule provided. Assessments will be performed on Day 10, in the clinic, as listed in Table 1.

NUMBER OF PATIENTS PLANNED:

Up to 60 MuSK-MG patients to complete the study, and a sample of 10 AChR-MG patients will be sought.

CRITERIA FOR INCLUSION AND EXCLUSION:

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

1. Willing and able to provide written informed consent after the nature of the study has been explained and before the start of any research-related procedures.
2. Male or female ≥18 years of age.
3. Positive serologic test for anti-MuSK antibodies or anti-AChR antibodies as confirmed at Screening or by previous antibody test, with report available.

4. Confirmatory electromyography (EMG) or EMG report.
5. Myasthenia Gravis Foundation of America (MGFA) Class II to IV at Screening.
6. MG-ADL score of ≥6 at Screening, with more than 50% of this score attributed to non-ocular items.
7. Patients receiving steroids and/or pyridostigmine should not have any modification of drug regimen during the month before Screening.
8. Female patients of childbearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG] at screening); and must practice an effective, reliable contraceptive regimen during the study and for up to 30 days following discontinuation of treatment.
9. Ability to participate in the study based on overall health of the patient and disease prognosis, as applicable, in the opinion of the Investigator; and able to comply with all requirements of the protocol, including completion of study questionnaires.

Individuals who meet any of the following Exclusion Criteria are not eligible to participate in the study:

1. Epilepsy and currently on medication.
2. Concomitant use of medicinal products with a known potential to cause QTc prolongation.
3. Patients with long QT syndromes.
4. History of thymectomy within 12 months before Screening.
5. An electrocardiogram (ECG) within 6 months before starting treatment that shows clinically significant abnormalities, in the opinion of the Investigator.
6. Breastfeeding or pregnant at Screening or planning to become pregnant at any time during the study.
7. Patients receiving immunomodulatory treatment (e.g. plasma exchange [PE], therapeutic plasma exchange [TPE], intravenous immunoglobulin G [IVIG]) should not have any treatment in the previous 4 weeks prior to Randomization or at any time during the study.
8. Use of rituximab or other similar biologic medications for immunomodulation within 6 months prior to Screening.
9. Treatment with an investigational drug (other than amifampridine), device, or biological agent within 60 days prior to Screening or while participating in this study.
10. Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the study, poses an added risk for the patient, or confound the assessment of the patient.
11. History of drug allergy to any pyridine-containing substances or any amifampridine excipient(s).

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

The investigational product (IP) is amifampridine tablets 10 mg, and it will be provided in round, white-scored tablets, containing amifampridine phosphate formulated to be the equivalent of 10 mg amifampridine base per tablet. Dosing is up to 80 mg/day in 3 or 4 divided doses.

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

REFERENCE THERAPY, DOSE, ROUTE, AND REGIMEN:

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

DURATION OF TREATMENT:

At least 38 days (excluding up to 14-day screening period). The Run-in phase requires that the patient must be on a stable dose and dose regimen for the last week of Run-in.

CRITERIA FOR EVALUATION:

Safety:

Safety will be assessed by the incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs). Vital signs, 12-lead ECGs, clinical laboratory tests, physical examination, and concomitant medications will also be evaluated.

Efficacy:

Efficacy will be assessed by comparison of amifampridine versus placebo for:

Primary -

- Change from baseline in MG-ADL total score;

Secondary -

- Change from baseline in QMG total score.
- Proportion of patients with at least a 2-point change from baseline in the MG-ADL score.
- Proportion of patients with at least a 3-point change from baseline in the QMG total score.

STATISTICAL METHODS:

Sample Size Determination

The study is powered with respect to the primary endpoint of change in MG-ADL score from baseline for the MuSK-MG group of subjects. The study has approximately 60% power to detect a 2 point difference between amifampridine and placebo treatment groups for the change in MG-ADL from baseline (Day 0).

Safety Analysis

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

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Only treatment-emergent AEs (TEAEs) will be included in the safety analysis. The incidence of TEAEs will be summarized by system organ class, preferred term, relationship to treatment, and severity by treatment group.

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

Subgroup analyses for safety will be performed independently on the MuSK-MG and AChR-MG groups. No pooled analyses are planned.

Efficacy Analysis

Efficacy analysis will be conducted on 2 datasets:

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

Primary endpoint efficacy analysis of the MuSK-MG group will be analyzed as the change in MG-ADL from baseline (Day 0) using the Wilcoxon-Mann-Whitney Rank sum test at a two sided α of 0.05 using the FAS population.

The first secondary endpoint of the MuSK-MG group will be analyzed as the change in QMG from baseline (Day 0) using the Mann-Whitney-Wilcoxon Rank sum test at a two sided α of 0.05 using the FAS population.

The next secondary endpoint of the MuSK-MG group will be analyzed as the proportion of subjects with a change of 2 or more points in MG-ADL score from baseline (Day 0), followed by proportion of subjects with a change of 3 or more points in the QMG score, using the Fischer's exact test at a two sided α of 0.05 using the FAS population.

AChR-MG subjects will only be evaluated by descriptive statistics.

Subgroup analyses for efficacy will be performed independently on the MuSK-MG and AChR-MG groups. No pooled analyses are planned.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

3,4-DAP	3,4-diaminopyridine
Abs	Antibodies
ACh	Acetylcholine
AChR	Acetylcholine receptor
AChR-MG	Acetylcholine receptor Myasthenia Gravis
ADL	Activities of Daily Living
ADME	absorption, distribution, metabolism, and excretion
AE(s)	adverse event(s)
AIN	adult idiopathic nystagmus
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
ANS	autonomic nervous system
AST	aspartate aminotransferase
ATU	Autorisations Temporaires d'Utilisation Normative
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to infinity
CI	confidence interval
C_{max}	peak plasma concentration
CMS	congenital myasthenia syndromes
CNS	central nervous system
CRA(s)	clinical research associate(s)
CRF	case report form
CRO	contract research organization
CYP450	cytochrome P450
DBP	diastolic blood pressure
ECG(s)	electrocardiogram(s)
eCRF	electronic case report form
EEG	electroencephalogram
EFNS	European Federation of Neurological Societies
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice

HCG	human chorionic gonadotropin
hERG	human Ether-à-go-go Related Gene
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IVIG	intravenous immunoglobulin G
K^+	potassium ion
kg	kilogram
LEMS	Lambert-Eaton myasthenic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MG-ADL	Myasthenia Gravis-Specific Activities of Daily Living
MG	Myasthenia Gravis
MGFA	Myasthenia Gravis Foundation of America
MI	myocardial infarction
mmHg	millimeters of mercury
MS	multiple sclerosis
MuSK	muscle-specific receptor tyrosine kinase
MuSK-MG	muscle-specific receptor tyrosine Kinase-Myasthenia Gravis
NAT	N-acetyl transferase
ng/mL	nanograms per milliliter
NMJ	neuromuscular junction
PE	plasma exchange
Pgp	P-glycoprotein
PI	Principal Investigator
PK	pharmacokinetic
PP	per protocol
QMG	quantitative myasthenia gravis
QT	QT wave
QTc	QT wave corrected for heart rate
REB	research ethics board

SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SBP	systolic blood pressure
SGI	subject global impression
SOPs	standard operating procedures
$t_{1/2}$	elimination half-life
TEAE(s)	treatment emergent adverse event(s)
TK	toxicokinetic
T_{max}	time to reach maximum plasma concentration
TPE	therapeutic plasma exchange
US	United States

Definition of Terms:

Investigational Product (IP):

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

5 ETHICS

5.1 Independent Ethics Committee / Institutional Review Board

Before initiating the study, the Investigator will obtain written confirmation that the institutional review board (IRB), independent ethics committee (IEC), or Research Ethics Board (REB) is properly constituted and compliant with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) requirements, applicable laws and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to Catalyst Pharmaceuticals, Inc. (Catalyst) or its designee. The Investigator will provide the IRB/IEC/REB with all appropriate material, including the protocol, Investigator's Brochure

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

5.2 Ethical Conduct of Study

This study will be conducted in accordance with the following:

- ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (ICH E6); and
- The ethical principles established by the Declaration of Helsinki.

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the risks. The rights and welfare of the patients will be respected and the Investigators conducting the study do not find the hazards to outweigh the potential benefits. Each patient will provide written, informed consent prior to any study-related tests or evaluations are performed.

5.3 Patient Information and Informed Consent

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

The Investigator will provide copies of the signed ICF to each patient and will maintain the original in the record file of the patient.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Before beginning the study, the Investigator must provide to Catalyst or designee, a fully executed and signed US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-investigators must be listed on Form FDA 1572 and provide a Financial Disclosure Form.

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

Laboratory evaluations will be performed at the local laboratory associated with the study site.

7 INTRODUCTION

A comprehensive review of amifampridine phosphate is contained in the Investigator's Brochure supplied by Catalyst (June 2017). Investigators are to review this document before initiating this study.

7.1 Disease Background

Myasthenia gravis (MG) is a rare, debilitating, acquired autoimmune disease of the neuromuscular junction (NMJ), caused by the failure of neuromuscular transmission, which results from the binding of autoantibodies (Abs) to proteins involved in signaling at the NMJ. The main proteins affected are acetylcholine receptor (AChR) and muscle-specific receptor tyrosine kinase (MuSK). Myasthenia gravis is clinically characterized by weakness and fatigability of skeletal muscles, with disease severity varying widely among affected patients. MuSK-MG is a disease characterized by a predominance in females, earlier onset than other AChR-MG, prominent bulbar involvement, more severe clinical condition, and significant resistance to treatment (Pasnoor, 2010). AChR-MG and MuSK-MG also have a different immunopathologic mechanisms, with IgG1 and IgG3 complement binding antibodies involved in the former, and IgG4 in the latter.

Although many patients with MuSK-MG are treated with anticholinesterase inhibitors or immunosuppressants, they do not respond well to such treatments. Hence, MuSK-MG patients may continue to have marked generalized weakness and bulbar signs and symptoms of the disease. In these patients, the search for alternative treatment strategies targeting different pathophysiologic aspects of the disease is a medical need.

The use of amifampridine in patients with MuSK-MG has been described for 2 children, who achieved some benefit (Skjei, 2013) and 1 adult (Evoli, 2016). Following 4 months of treatment, the authors report the adult patient had obvious improvement of ptosis, decreased neck weakness and arm fatigability.

An Investigator-Sponsored MuSK-MG study in Italy involved a randomized, placebo-controlled crossover design in patients receiving amifampridine phosphate and placebo. Seven MuSK-MG patients were enrolled in the study. In the open-label run-in period amifampridine phosphate dose was titrated upward, at the discretion of the Investigator, for a minimum of 3 weeks, with the last week showing stable dose and frequency. At the end of this period, patients must show a 3-point improvement in Myasthenia Gravis Composite (MGC) scale to be eligible for randomization. In Treatment Period 1, patients were randomized to receive either amifampridine tablets or placebo tablets for 1 week. After completion of Treatment Period 1, in Treatment Period 2 patients were administered the test medication they did not receive in Treatment Period 1, under double-blind conditions. In Treatment Period 3, they received the same medication as in Treatment Period 1.

The results of this approximately 50 day study demonstrated the Musk-MG patients had statistically significant higher functional performance in all the validated assessment scales when they were administered amifampridine compared to placebo. Overall, the results demonstrated a consistent high level of efficacy with amifampridine in MuSK-MG patients, and excellent tolerability.

7.2 Amifampridine

Amifampridine (3,4-DAP) is a non-specific voltage-dependent potassium (K^+) channel blocker. Blockade of K^+ channels causes depolarization of the presynaptic membrane and slows down or inhibits repolarization. Prolonged depolarization results in opening of slow voltage-dependent calcium (Ca^{2+}) channels and allows a subsequent influx of Ca^{2+}. The increased concentration of intracellular Ca^{2+} induces exocytosis of the synaptic vesicles containing acetylcholine (ACh), thus releasing an increased level of ACh into the synaptic cleft (Maddison, 1998a; Maddison, 1998b). The influx of ACh into the presynaptic cleft enhances neuromuscular transmission, providing improved muscle function.

Over the last 25 years, a considerable amount of clinical experience with amifampridine has been gained, which provides a strong body of evidence for its efficacy and safety in the treatment of patients with neurologic disorders, including MG, Lambert-Eaton myasthenic syndrome (LEMS), multiple sclerosis (MS), congenital myasthenia syndromes (CMS), downbeat nystagmus, and amyotrophic lateral sclerosis (ALS). Amifampridine has been recommended as first-line symptomatic treatment for LEMS by the European Federation of Neurological Societies (EFNS) (Skeie, 2006; Skeie, 2010; Lindquist, 2011) and amifampridine tablets 10 mg (as amifampridine phosphate) (Firdapse® Tablets) is marketed for the treatment of LEMS in the European Union (including Norway and Iceland), Israel, and Switzerland. The collective body of data indicates that amifampridine/ amifampridine phosphate is well tolerated up to and including 80 mg/day (Firdapse Investigator Brochure, June 2017).

Recent nonclinical publications are supportive of exploration of amifampridine in myasthenia gravis caused by antibodies against muscle-specific kinase (MuSK). Mori and colleagues (2012) found that amifampridine (3,4-DAP) significantly improved neuromuscular transmission by predominantly increasing ACh release in the neuromuscular junction of MuSK-MG mice, demonstrating that the presynaptic defect (plus a smaller postsynaptic effect) could contribute to failure of neuromuscular transmission. In Morsch and colleagues study (2013) using a mouse model of MuSK-MG, amifampridine (3,4-DAP) significantly enhanced neuromuscular transmission after 1 week of treatment without exacerbating loss of endplate AChRs, whereas pyridostigmine exacerbated neuromuscular impairment. Clinical evidence also demonstrates that amifampridine produces improvement in MuSK-MG (Evoli, 2016).

7.3 Nonclinical Studies

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

- Five safety pharmacology studies in central nervous system (rat), respiratory (rat), and cardiovascular (telemeterized dogs, *in vitro* human Ether-à-go-go Related Gene (hERG) and rabbit Purkinje fiber)
- Pharmacokinetics and mass balance in rat and dog
- *In vitro* metabolism in human and animal hepatocytes
- Human hepatic cytochrome P450 (CYP450) inhibition and induction

- Human P-glycoprotein (Pgp) interaction
- Single dose toxicity and toxicokinetic (TK) studies in mouse and rat
- Repeat dose toxicity and toxicokinetic in rat (28-day, 13-week, and 2 years) and dog (28-day and 9-month)
- Reproductive and developmental toxicity in rat and rabbit
- Six *in vitro* and *in vivo* genotoxicity studies

The main nonclinical findings were CNS and autonomic nervous system (ANS) effects, the development of Schwannomas, and histologic changes in muscle tissues after administration of amifampridine.

7.4 Previous Clinical Studies

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

7.4.1 Amifampridine Phosphate in Healthy Subjects

A first in human Phase 1 study (DAPSEL Study, 2006) with amifampridine phosphate was conducted to investigate the bioavailability/bioequivalence and tolerability of amifampridine administered as a phosphate salt or free base. In the first part of the study, a pilot tolerance study was conducted in 5 healthy male volunteers who received a single 10-mg dose of amifampridine phosphate to determine tolerability. In the second part of the study, bioequivalence testing was conducted in 27 healthy male volunteers. Each patient was randomized to receive either a single dose (2 × 10 mg tablets) of amifampridine as amifampridine phosphate or amifampridine base and received alternate treatment following a minimum of 72-hour washout period.

This study demonstrated bioequivalence for area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$), with the 90% confidence interval (CI) for the base/salt ratio of 93.1% to 113.3% falling within the predefined limits of 90% to 125% for bioequivalence. The mean elimination half-life ($t_{1/2}$) of amifampridine was 1.8 hours for the phosphate and 1.6 hours for the free base form. Amifampridine C_{max} was 64.8 ng/mL for the phosphate and

57.0 ng/mL for the free base form. Potentially improved absorption of the phosphate salt explained the slightly higher C_{max} observed for amifampridine phosphate compared with the free base. All adverse events (AEs) were mild or moderate, transitory and fully reversible. The nature and frequency of side-effects did not differ between formulations (phosphate salt or base). The most common AE (25 of 40 AEs) was paresthesia, which was mainly minor peri-oral paresthesia. Since paresthesia is well recognized as an AE occurring in patients treated with amifampridine, all were considered as possibly related to investigational product (IP) by the Investigator. The only other AE occurring in >1 patient and judged possibly related to amifampridine was abdominal pain (4 events). Simple flu (5 events) and feeling of discomfort (2 events) were also reported for > 1 patient in the study, however were considered not related to amifampridine treatment.

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

A Phase 1 study (LMS-001) in healthy volunteers evaluated whether food consumption significantly affected the bioavailability of amifampridine phosphate tablets. This was an open-label, randomized, single-dose, 2-treatment, 2-period crossover design in 46 healthy volunteers. Each patient received 20 mg amifampridine phosphate on 2 occasions, once fasting and once after consumption of a standard high fat breakfast. The 2 single 20 mg doses of amifampridine phosphate were administered 6 days apart. Data indicate that taking amifampridine with food reduces exposures determined by C_{max} (maximum serum levels) by approximately 40% and AUC by approximately 20%. In addition, the time to maximum serum concentrations (T_{max}) was increased 2-fold from approximately 38 minutes (fasted) to 78 minutes (fed). The drug was well tolerated with no serious adverse events and only 1 severe event, an episode of gastroenteritis unrelated to amifampridine. The most common adverse events occurring in ≥ 10% of patients were: oral paresthesia (20 patients; 43%), peripheral paresthesias (12; 26%), dizziness (5; 11%), headache (5; 11%), and oral hypoesthesia (5; 11%). Abdominal pain, nausea, peripheral paresthesias, dizziness, and headache were more commonly reported by patients following administration of amifampridine phosphate in the fasted state.

In both Study LMS-001 and DAPSEL, PK parameters were highly variable with 10-fold ranges observed in values of C_{max}, AUC, and $t_{½}$ across patients. In humans, amifampridine is

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

7.4.2 Efficacy of Amifampridine

A Phase 3, randomized, double-blind, placebo-controlled study (LMS-002) evaluated the efficacy and safety of amifampridine tablets 10 mg, as amifampridine phosphate (30-80 mg total daily dose) versus placebo in patients with LEMS. The study has 4 parts, with the first 3 parts complete in the clinic (open-label extension ongoing). Patients treated with amifampridine phosphate had statistically significant improvement in both primary efficacy measures relative to patients treated with placebo. The change in QMG scores from baseline (Day 1, Part 2) to Day 14 (Part 3) reached statistical significance (p=0.0452), with the least square (LS) mean for QMG score increasing by 2.2 in placebo-treated patients, and increasing by 0.4 in amifampridine-treated patients. For the other primary endpoint, subject global impression (SGI), patients who were receiving amifampridine on Day 1 reported, on average, that they were "pleased" (SGI score of 5.9 ± 1.2) with the test medication while they were receiving it. After being switched to placebo tablets, their opinions dropped, on average, 2.7 ±2.3 points. The LS mean was -2.6 for the placebo group and -0.8 for the amifampridine group, a difference of 1.8 ±0.6 (p=0.0028), corresponding to a patient assessment, of "mixed" for the placebo tablets. This substantial change in patients'

assessments, to a worsening of their condition while receiving placebo, was considered clinically significant.

In addition to Study LMS-002, 5 randomized, double-blind, placebo-controlled studies and 1 double-blind study with an active comparator (reported in abstract form only) in 71 patients with LEMS are reported in the clinical literature. In all 6 studies, amifampridine (in base form) was shown to be more effective for the symptomatic treatment of LEMS compared with placebo or active comparator across a number of independent measures of neurological function. Supportive data from multiple published uncontrolled investigations and case reports demonstrate the long-term benefits of treatment with amifampridine in patients with LEMS, and show that removal of patients from drug has led to recurrence of underlying symptoms. Refer to the Firdapse Investigator Brochure (June 2017) for further details on these studies.

7.4.3 Safety of Amifampridine and Amifampridine Phosphate

Safety data collected from 1,454 patients or healthy volunteers in controlled study LMS-002 (LEMS), controlled and uncontrolled published studies of LEMS or other neurologic conditions, a 3-year safety surveillance study (ATU), and PK studies demonstrate amifampridine is well tolerated up to and including 80 mg/day (Firdapse Investigator Brochure, June 2017). The most common adverse events observed from the clinical safety data were perioral and peripheral paresthesias and gastrointestinal disorders (abdominal pain, nausea, diarrhea, epigastralgia). These events were typically mild or moderate in severity, and transient, seldom requiring dose reduction or withdrawal from treatment. In the pharmacogenomic study in healthy subjects (classified as either slow acetylators or fast acetylators), slow acetylators experienced >80% more drug-related AEs compared with fast acetylators (FIR-001).

Clinically significant or serious adverse events were infrequent in all studies for all indications. A total of 12 deaths were reported in the 1,454 patients or healthy subjects. Six of 12 deaths were associated with accompanying malignancy (1 of 6 with pulmonary embolus as terminal event), 1 due to tracheobronchitis, and 2 due to myocardial infarction (MI). Attribution to amifampridine for 2 of 3 deaths from the ATU study was specified as unrelated; causality for the third death was not reported. No attribution was specified in the academic series, but the author singled out the fatal MI as the only serious incident during amifampridine therapy, implying that the 2 deaths due to malignancy, the 1 due to malignancy and pulmonary embolus and the 1 due to tracheobronchitis were not related in his opinion. The author further states that no pathological findings related to amifampridine

were found in the patient who died of tracheobronchitis. For 1 of the fatal MIs, the author speculates that a "sudden increase of physical activity" with amifampridine may have been a contributant (Lundh, 1984; Lundh, 1993); no causality was reported for the other fatal MI (Bertorini, 2011). Three deaths occurred in children with CMS, including 2 with fast-channel CMS (Beeson, 2005). Although no causal relationship was established with amifampridine, the authors advise its use cautiously in children and in fast-channel patients. The other CMS death was not thought to be related to amifampridine (Palace, 1991). Overall 7 of 12 deaths were not considered related to amifampridine; neither cause nor causality is known for 4 deaths; and amifampridine may have contributed indirectly to 1 of the MI-related deaths.

The most frequent clinically significant or serious event was seizure. A total of 10 (0.69%) patients out of 1,454 patients or healthy subjects experienced seizures or convulsions after treatment with amifampridine. Electroencephalogram (EEG) findings, reported for 3 of the 10 patients, did not show epileptiform activity. Three of 10 seizures occurred in patients with LEMS (3/209; 1.44%), 4 occurred in patients with MS (4/774; 0.5%), 1 occurred in a patient with CMS (1/88; 1.14%) (Harper, 2000) and 2 seizures were reported in a literature-based study where both MG and LEMS patients were enrolled, but the paper did not state the indication (Sanders, 1993; Sanders, 2000; Flet, 2010; McEvoy, 1989; Boerma, 1995; Bever, 1996).

Three patients experienced seizures on a daily dose of ≥90 mg/day (n=3; LEMS or MG). No other cause was apparent in 2 cases; 1 patient had concurrent toxic serum levels of theophylline (McEvoy, 1989; Sanders, 1993). A fourth patient with LEMS had multiple seizures following accidental ingestion of 360 mg/day amifampridine for 7 days (prescribed dose 60 mg/day) (Boerma, 1995). There were potentially contributing conditions in 6 patients, specifically, concurrent treatment with theophylline (n=1; LEMS or MG), or coexistent brain metastases (n=1; LEMS), epilepsy (n=1; MS) and MS (n=4). In cases where follow-up was reported, most seizures did not recur with amifampridine dose reduction or treatment withdrawal. In the one accidental overdose case, seizures were controlled with intravenous clonazepam and the patient made a full recovery (Boerma, 1995). Note that a seizure rate of 4% can be expected in the natural course of patients with MS (Engelsen, 1997; Moreau, 1998; Kinnunen, 1987). Among the 774 MS patients treated with amifampridine included in the safety assessment of this report, 4 (0.5%) experienced seizures.

Other clinically significant or SAEs reported in more than 1 patient were palpitations (8/1,454; 0.56%), abnormal liver enzymes (6/1,454; 0.41%), QTc prolongation (2/1,454; 0.14%), and premature ventricular contraction/increased ventricular extrasystoles (2/1,454;

0.14%). Each of the following serious or clinically significant events was reported in a single patient: chorea, paresthesias, paroxysmal supraventricular tachycardia, cardiac arrest, drug-induced hepatitis, gastroesophageal reflux, increased lipase and amylase, aspiration pneumonia with confusion, and urinary tract infection with confusion.

7.5 Overall Risks and Benefits

Data on amifampridine treatment in 1,454 patients or healthy volunteers support the favorable safety profile of amifampridine (both base and phosphate formulations) at doses up to 80 mg per day. Current data demonstrate that amifampridine phosphate salt has an acceptable tolerability profile with a positive risk-benefit in patients treated with amifampridine. Refer to the Investigator's Brochure (June 2017) for further discussion on benefit/risk of amifampridine.

7.6 Study Rationale

As discussed above in Section 7.4, a considerable amount of clinical experience is available with amifampridine (3,4-diaminopyridine; 3,4-DAP) and, in December 2009, amifampridine tablets 10 mg, as amifampridine phosphate, received marketing approval by the European Commission as Firdapse® for the symptomatic treatment of patients with LEMS. Case reports, animal data and a pilot controlled clinical trial suggest that amifampridine may also have clinical utility in patients with MuSK-MG. Thus, the purpose of this study (MSK-002) is to demonstrate the safety and efficacy of amifampridine in patients with MuSK-MG. There is the possibility that amifampridine phosphate may also have a beneficial effect on AChR-MG, though immunopathalogically, clinically, and in responsiveness to medication the diseases appear different. To explore this, a sample (N=10) of AChR-MG patients, who meet the inclusion criteria, will attempt to be recruited.

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objectives of the study are:

- To characterize the overall safety and tolerability of amifampridine compared with placebo in patients with MuSK-MG; and
- To assess the clinical efficacy of amifampridine compared with placebo in patients with MuSK-MG, and a sample of patients with AChR-MG, based on change from baseline in the Myasthenia Gravis Activities of Daily Living (MG-ADL) scores.

8.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the clinical efficacy of amifampridine compared with placebo by using the change from baseline in total Quantitative Myasthenia Gravis (QMG) score;
- To assess the safety and efficacy of amifampridine compared with placebo in a sample of patients with AChR-MG (N equal to 10).

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a stratified, randomized (1:1), double-blind, placebo-controlled, parallel group, outpatient study designed to evaluate the safety, tolerability and efficacy of amifampridine in patients diagnosed with MuSK-MG and a sample of AChR-MG patients. The study is planned to be conducted at up to 20 sites in US, Europe, and Canada; and will include about 60 male and female MuSK-MG patients, and 10 AChR-MG patients. If it is determined that 18 or more of the first 20 screened AChR-MG patients fail to meet inclusion criteria, additional screening for AChR-MG patients will be terminated. If the AChR-MG screening failure rate is lower, an additional 20 patients will be screened; overall, up to 40 AChR-MG patients may be screened to try and enroll 10 in the study.

The planned duration of participation for each patient is at least 38 days excluding the screening period, which can last up to 14 days. In addition to amifampridine tablets, 10 mg, as amifampridine phosphate, patients will continue to receive stable dose of pyridostigmine and/or corticosteroids, but no changes to medications are permitted during the study.

All patients who sign an informed consent will be screened for eligibility to participate in the study: inclusion and exclusion criteria; medical and medication history; complete physical exam (including vital signs, height, weight); standard 12-lead ECG; clinical laboratory testing; serum pregnancy testing (females of childbearing potential only; result must be negative to proceed into the run-in period with open-label IP administration); MuSK or AChR antibody testing (if not previously done and report available); EMG (if not previously done and report available); and assessment of serious adverse events (SAEs) (Table 1).

Those patients successfully completing screening will have procedures/assessments (see Table 1) conducted at the start of the Run-in period (Day 1, before starting medication) and during run-in, until stable dose and frequency of amifampridine is established for at least 7

days, and at least a 2-point improvement in MG-ADL score is achieved. Screening and the start of the Run-in period may be combined into a single visit, in which case overlapping procedures/assessments will only need to be performed once. On the last day of the Run-in period (Day 0), procedures/assessments, as detailed in Table 1, will be conducted to confirm eligibility for randomization, including a negative pregnancy test. Every attempt should be made to have the same individual perform all assessments for a patient throughout the study.

Randomized patients will be assigned to one of 2 treatment groups under double-blind conditions; either placebo or amifampridine phosphate.

Open-label Run-in

Amifampridine dose will be titrated upward every 3 to 4 days, starting at 10 or 15 mg/day, at the discretion of the Investigator. Patients will either visit or have telephone/video contact with the site for each dose titration and at least one in-person site evaluation at Week 3 of the run-in period. When the Investigator determines that the patient has reached the maximal tolerable and efficacious dose, the patient should demonstrate they can remain on a stable dose and frequency for at least an additional 7 days. The Open-label Run-in period may be extended if additional time is needed for the dose titration. At the end of this period, patients must show at least a 2-point improvement in MG-ADL from start of Run-in, to be eligible for randomization (Day 0).

Randomization

Patients who continue to meet all the inclusion and exclusion criteria will be randomized on the last day of the Run-in period (Day 0).

Period 1 (Days 1-10) (+1 day)

Patients who have successfully completed the Open-label Run-in and continue to meet all inclusion/exclusion criteria will be randomized (1:1 ratio) on Day 0 to receive either amifampridine tablets (10 mg as amifampridine phosphate) or placebo tablets for 10 days, under double-blind conditions, (blinded medication to start after assessments obtained on open-label medication, on Day 0). Test medication will be dispensed by the site pharmacist, according to the randomization schedule provided by Sponsor. All unused medication and the container must be brought back to the study site at the end of Period 1. Safety and efficacy assessments will be made, in the site clinic, on Day 10 as detailed in the Schedule of Assessments in Table 1 and Section 12.

Table 1. Schedule of Events

Study Assessment or Event [b]	Screening	Run-in		Period 1 (Days 1-10)
		Start [a]	Last Visit	
	Days -14 to -1	Start of Run-in	Day 0[j] end of Run-in	Day 10[j] (+1 d)
Informed consent [c]	X			
Inclusion/Exclusion Criteria	X		X	
Randomization			X	
Medical history	X		X [d]	
Complete physical exam [e]	X		X	X
Vital signs [f]	X		X	X
12-Lead ECG [g]	X		X	
Clinical laboratory tests [h]	X		X	
Pregnancy test [i]	X		X	X
MuSK and/or AChR Antibody testing	X[n]			
EMG	X[n]			
IP Treatment Administration [j]		X	X	Daily
Dispense blinded IP [k]			X	
IP accountability		X	X	X
Myasthenia Gravis-Specific Activities of Daily Living (MG-ADL)	X	X [l]	X [l]	X
Quantitative Myasthenia Gravis (QMG) score	X	X [l]	X [l]	X
Adverse events/SAEs [m]	X	X	X	X
Concomitant medications	X	X	X	X
Urine drug screen				X
Patient Dosing Diary Provided		X	X	

ECG = electrocardiogram; EMG = electromyography; IP = investigational product (amifampridine or placebo); SAE = serious adverse event

[a] Titrate from starting dose of 10-15 mg/day, every 3 to 4 days with at least one site visit at Week 3. Last week of run-in, study drug dose and frequency must be stable before being eligible for randomization on Day 0.

[b] All safety assessments (vital signs, ECGs, laboratory tests) are to be performed **before the dose taken in the study clinic** unless specified otherwise. All efficacy assessments will be performed at standardized times relative to the dose that must be taken in the study clinic on Days 0 and 10, according to the efficacy assessments schedule in Section 9.7

[c] Informed consent must be obtained before any study procedures are performed.

[d] Any changes since the Screening Visit will be noted.

Table 1. Schedule of Events

Study Assessment or Event [b]	Screening	Run-in		Period 1 (Days 1-10)
		Start [a]	Last Visit	
	Days -14 to -1	Start of Run-in	Day 0[j] end of Run-in	Day 10[j] (+1 d)

[e] Complete physical examination includes evaluation of all major body systems, including weight at all visits and height at Screening only (Section 9.6.6).
[f] The time of the last dose should be recorded in relation to taking Vital signs.
[g] The time of the last dose should be recorded in relation to performing Standard 12-lead safety ECGs.
[h] Clinical laboratory tests include serum chemistry, hematology, and urinalysis.
[i] Serum pregnancy tests will be obtained from female patients of childbearing potential only at Screening; urine dipstick may be used for the remainder of the study.
[j] IP will be administered by the clinic staff during in-clinic visit so assessments can be timed according to IP administration.
[k] Patients will be provided blinded packages containing amifampridine or placebo depending on their randomized sequence of treatment. Collect all open-label medication.
[l] Assessment only at the first (Day 1) and last (Day 0) run-in visits.
[m] SAE reporting commences when informed consent is signed. Non-serious adverse event reporting commences on Day 1 of run-in (Section 10).
[n] If not previously done and report available.

9.2 Selection of Study Population

Criteria for participation in the study are provided in Sections 9.2.1 and 9.2.2.

9.2.1 Inclusion Criteria

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

1. Willing and able to provide written informed consent after the nature of the study has been explained and before the start of any research-related procedures.
2. Male or female ≥18 years of age.
3. Positive serologic test for anti-MuSK antibodies or anti-AChR antibodies as confirmed at Screening or by previous antibody test, with report available.
4. Confirmatory EMG or EMG report.
5. Myasthenia Gravis Foundation of America (MGFA) Class II to IV at Screening.
6. MG-ADL score of ≥6 at Screening, with more than 50% of this score attributed to non-ocular items.
7. Patients receiving steroids or pyridostigmine should not have any modification of drug regimen during the month before Screening.
8. Female patients of childbearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG] at screening); and must practice an effective, reliable contraceptive regimen during the study and for up to 30 days following discontinuation of treatment.
9. Ability to participate in the study based on overall health of the patient and disease prognosis, as applicable, in the opinion of the Investigator; and able to comply with all requirements of the protocol, including completion of study questionnaires.

9.2.2 Exclusion Criteria

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

1. Epilepsy and currently on medication.
2. Concomitant use of medicinal products with a known potential to cause QTc prolongation.

3. Patients with long QT syndromes.
4. History of thymectomy within 12 months before Screening.
5. An electrocardiogram (ECG) within 6 months before starting treatment that shows clinically significant abnormalities, in the opinion of the Investigator.
6. Breastfeeding or pregnant at Screening or planning to become pregnant at any time during the study.
7. Patients receiving immunomodulatory treatment (e.g. plasma exchange [PE], therapeutic plasma exchange [TPE], intravenous immunoglobulin G [IVIG]) should not have any treatment in the previous 4 weeks prior to Randomization or at any time during the study.
8. Use of rituximab or other similar biologic medications for immunomodulation within 6 months prior to Screening.
9. Treatment with an investigational drug (other than amifampridine) or device within 30 days before Screening or while participating in this study.
10. Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the study, poses an added risk for the patient, or confound the assessment of the patient.
11. History of drug allergy to any pyridine-containing substances or any amifampridine excipient(s).

9.2.3 Removal of Patients from Treatment or Assessment

Patients may withdraw their consent to participate in the study or to receive treatment with IP at any time without prejudice. The Investigator must withdraw from the study or from treatment with IP any patient who requests to be withdrawn. A patient's participation in the study or treatment with IP may be discontinued at any time at the discretion of the Investigator and in accordance with his or her clinical judgment.

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

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

- Patient experiences a serious or intolerable AE;
- Patient requires medication prohibited by the protocol; and
- Patient becomes pregnant (refer to Section 10.4 for details on the reporting procedures to follow in the event of pregnancy).

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

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

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

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

9.2.4 Patient Identification

Each patient will be assigned a unique patient identifier (2 or 3 digits for the site and 2 or 3 digits for each patient enrolled). This unique identifier will be on all CRF pages.

9.2.5 Re-screening

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

Labs do not have to be repeated for 60 days, except for pregnancy test. Patients may be replaced if terminated after randomization.

9.3 Treatments

9.3.1 Treatments Administered

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

Investigational product: Amifampridine tablets 10 mg will be provided in round, white-scored tablets and containing amifampridine phosphate formulated to be the equivalent of 10 mg amifampridine base per tablet. The product will be provided in bottles of bulk tablets to the pharmacy representative who will dispense an amount for each portion of the study, in a patient-specific labeled bottle.

Placebo: A placebo equivalent will be provided as tablets indistinguishable from the amifampridine tablets. The placebo will be administered consistent with the dose regimen of amifampridine. The placebo tablets will be provided in bottles of bulk tablets to the pharmacy representative, who will dispense an amount, in a patient-specific labeled bottle.

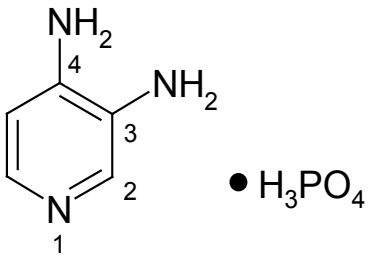
9.3.2 Identity of Investigational Product

The chemical name of amifampridine phosphate is:

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

The chemical structure is provided in Figure 1.

Figure 1. Chemical Structure of Amifampridine Phosphate



9.3.2.1 Product Characteristics and Labeling

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

The tablets are to be dispensed by the site pharmacy representative into suitably sized pharmacy containers for patient use. Placebo will be provided as tablets indistinguishable from amifampridine, sent to the research pharmacy representative. The amifampridine tablets and placebo tablets will be clearly labeled as to their identity, and the pharmacist is responsible for dispensing the amifampridine tablets or placebo tablets, as needed, for each patient.

Each bottle provided to patients will be labeled to include the compound name, site number, patient ID number, date dispensed, storage instructions, the statement 'Caution – New Drug – Limited by Federal law to investigational use,' trial number, manufacturer name and address, and area for instructions for use. Any additional regional label requirements and translations will be included in accordance with local regulations.

9.3.2.2 Storage

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

9.3.3 Directions for Administration

All doses of study treatment will be taken at home, except one of the doses on the day of the in-clinic study visits, when it will be administered by study personnel and will be administered in the clinic to facilitate timing of efficacy assessments. Test medication should be taken every day at approximately the same time, at the dose and frequency instructed by Investigator. On the day of an in-clinic study visit (Days 0 and 10), dose administration will be the medication the patient has been taking for the previous days, but administered by the study personnel 45 minutes before the first efficacy assessment. If the patient takes the dose three times a day, the patient should be given specific instructions on dosing relative to the

time of their visit to assure a dose will be given during the in-clinic visit within the required time window. All safety assessments will be performed before the dose administered to the patient during the in-clinic visit. Efficacy assessment will be performed at standardized times relative to the dose administered in the clinic.

Assessment	Start Time After Dose (+ 10 minutes unless otherwise specified)
MG-ADL	45 minutes
QMG	After MG-ADL

The dose of amifampridine will be individually determined by the Investigator, within the bounds of a total daily dose of 30 mg to 80 mg, divided into doses taken 3 to 4 times per day as prescribed by the Investigator, based on optimal neuromuscular benefit. The maximum single dose is 20 mg. Amifampridine dose will be titrated upward every 3 to 4 days, starting at 10 or 15 mg/day, at the discretion of the Investigator. Patients will either visit or have telephone/video contact with the site for each dose titration and at least one in-person site evaluation at Week 3 of the run-in period. When the Investigator determines that the patient has reached the maximal tolerable and efficacious dose, the patient should demonstrate they can remain on a stable dose and frequency for at least an additional 7 days. The Open-label Run-in period may be extended if additional time is needed for dose titration. At the end of this period, patients must show a ≥2-point improvement in MG-ADL from start of Run-in, to be eligible for randomization (Day 0).

9.3.4 Method of Assigning Patients to Treatment Groups

Patients will be stratified according to the type of MG (MuSK or AChR), randomized on the last day of the open-label run-in period (Day 0), in a 1:1 ratio, to either amifampridine or placebo. IP will be administered under double-blind conditions. Randomized patients who discontinue after initiation of treatment may be replaced.

The randomization code will be provided by an Interactive Web Randomization System (IWRS) to the site Pharmacist. Details will be included in the Pharmacy Manual.

9.3.5 Selection of Doses Used in the Study

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

9.3.6 Blinding

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

9.3.7 Treatment Compliance

Patients will be instructed to complete a Dosing Diary of study medication taken and return the Diary, all IP containers and remaining test medication at each study visit. Patient compliance with the dosing regimen will be assessed by reconciliation of the used and unused IP. The quantity dispensed, returned, used, lost, etc., must be recorded on the medication dispensing log provided for the study.

9.3.8 Investigational Product Accountability

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

9.3.9 Return and Disposition of Clinical Supplies

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

Unused IP may be destroyed on site, per the site's standard operating procedures, but only after Catalyst has granted approval for drug destruction. The monitor must account for all IP in a formal reconciliation process prior to IP destruction. All IP destroyed on site must be documented. Documentation must be provided to Catalyst and retained in the Investigator study files. If a site is unable to destroy IP appropriately, the site can return unused IP to Catalyst upon request. The return of IP or IP materials must be accounted for on a Study Drug Return Form provided by Catalyst.

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

9.4 Prior and Concomitant Medications

All prescription and over-the-counter medications and herbal and nutritional supplements taken by a patient for 14 days before the Screening visit will be recorded on the designated CRF. Additionally, the stop date of any medications the patient was taking within 6 months before Screening that are excluded or restricted by the protocol will be recorded.

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

Medications prohibited during the study are listed in Table 2.

Table 2. Medications Prohibited During Study

Immunomodulatory treatment (e.g. plasma exchange [PE], therapeutic plasma exchange [TPE], intravenous immunoglobulin G [IVIG]) should not be given in the previous 4 weeks prior to Randomization or at any time during the study.
Rituximab or similar biological medication within 6 months before Screening or during the study.
Any investigational product (other than amifampridine) or an investigational medical device within 60 days before Screening.

Concomitant use of amifampridine with medicinal products with atropinic effects may reduce the effect of amifampridine, which should be taken into consideration.

9.5 Dietary or Other Protocol Restrictions

9.5.1 Dietary Restrictions

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

9.5.2 Contraception

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

9.6 Safety Variables

Safety in this study will be determined from evaluation of AEs/SAEs, vital signs assessments, clinical laboratory assessments, ECGs, and physical examinations. Pregnancy testing is also required for females of childbearing potential. The timing of the required evaluations is described in the Schedule of Events in Table 1 and in Section 12.

9.6.1 Adverse Events

The determination, evaluation and reporting of AEs will be performed as outlined in Section 10.

9.6.2 Vital Signs

Specific visits for obtaining vital signs are provided in Table 1 and in Section 12. Vital signs will be measured while in a sitting position, after resting for 5 minutes, and include SBP and DBP measured in millimeters of mercury (mmHg), heart rate in beats per minute, respiration rate in breaths per minute. Weight (kg) and temperature in degrees Celsius (°C) will also be measured. Clinically significant changes from baseline will be recorded as AEs.

9.6.3 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 1 for the tests required by Protocol. The scheduled clinical laboratory tests are listed in Table 3.

All abnormal clinical laboratory result pages should be initialed and dated by an Investigator, along with a comment for each abnormal result indicating whether or not it is clinically significant. Any abnormal test results determined to be clinically significant by the Investigator should be repeated (at the Investigator's discretion) until the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the Investigator determines that the abnormal value is no longer clinically significant.

Each clinically significant laboratory result should be recorded as an AE. The diagnosis, if known, associated with abnormalities in clinical laboratory tests that are considered clinically significant by the Investigator will be recorded on the AE CRF.

Table 3. Clinical Laboratory Tests

Blood Chemistry	Hematology	Urine Tests	Other
Albumin Alkaline phosphatase ALT (SGPT) AST (SGOT) Direct bilirubin Total bilirubin BUN Calcium Chloride Total cholesterol CO_2 Creatine phosphokinase Creatinine Glucose GGT LDH Phosphorus Potassium Total protein Sodium Uric acid	Hemoglobin Hematocrit WBC count RBC count Platelet count Differential cell count	Appearance Color pH Specific gravity Ketones Protein Glucose Bilirubin Nitrite Urobilinogen Hemoglobin Urine drug screen (Day 10 only)	Pregnancy test, if applicable

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CO_2, carbon dioxide; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; WBC, white blood cell.

9.6.4 Pregnancy Testing

Female patients of childbearing potential will have a serum (at Screening) or urine pregnancy test at any other time points specified in the Schedule of Events (Table 1) and in Section 12. Female patients with a positive pregnancy test at Screening do not meet eligibility criteria for enrollment. Additional pregnancy tests will be performed at any visit in which pregnancy status is in question.

Refer to Section 10.4 for details on the reporting procedures to follow in the event of pregnancy.

9.6.5 Electrocardiogram (ECG)

A standard 12-lead safety ECG (single tracing) will be recorded with the patient resting comfortably in the supine position at the time points specified in the Schedule of Events (Table 1) and in Section 12. Clinically significant changes from baseline will be recorded as AEs.

9.6.6 Physical Examination

A complete physical examination is to be performed at each clinic visit or, if applicable, at early discontinuation from the study. Complete physical examination will include assessments of general appearance as well as the following:

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

Weight (kg.) will be measured with each physical examination throughout the study. Height (cm.) will be measured at screening only.

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

9.7 Efficacy Variables

The timing of required evaluation is described in the Schedule of Events in Table 1 following the sequence listed below.

Assessment	Start Time After Dose (± 10 minutes unless otherwise specified)
MG-ADL	45 minutes
QMG	After MG-ADL

9.7.1 Myasthenia Gravis-Specific Activities of Daily Living (MG-ADL)

The MG-ADL is a self-report scale designed to assess the patient's MG symptoms and functional performance of activities of daily living. The MG-ADL consists of 8 items (derived from symptom-based components of the original 13-item Quantitative Myasthenia Gravis test) to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item) and gross motor or limb (2 items) impairment related to effects from MG (Appendix 1). Each of the 8 items is rated using a response scale ranging from 0 (normal) to 3 (most severe). Lower scores indicate better functional performance. In this trial, the recall period for MG-ADL will be the preceding 9 or 10 days.

9.7.2 Quantitative Myasthenia Gravis (QMG)

The QMG score will be used to assess the patient's general body strength and fatigability Appendix 2). (The QMG will be administered at the protocol specified time points by the same evaluator throughout the study. Detailed instructions for the QMG assessment are provided in the MSK-002 Study Reference Manual.

10 REPORTING ADVERSE EVENTS

10.1 Adverse Events

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

- AEs not previously observed in the patient, that emerge during the study.

- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions.

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

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

The study period during which all non-serious AEs will be reported begins after the first administration of study drug through the termination visit or at the early termination visit. After informed consent but prior to initiation of study treatment, only SAEs associated with any protocol-imposed interventions will be reported. The criteria for determining, and the reporting of SAEs is provided in Section 10.2.

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

The Investigator responsible for the care of the patient or qualified designee will assess AEs for severity, relationship to IP, and seriousness (refer to Section 10.2 for SAE definition). Severity (as in mild, moderate or severe headache) is not equivalent to seriousness, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

The Investigator will determine the severity of each AE using grades defined in Table 4 (the event will be recorded on the source documents and AE CRF). Events that are Grades 4 and 5 are serious events and require completion of both an SAE form and AE CRF.

Table 4. Categories of Severity for Adverse Events

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

Activities of Daily Living (ADL)

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

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

The Investigator will suggest the relationship of an AE to the IP and will record it on the source documents and AE CRF, using the relationship categories defined in Table 5.

Table 5. Description of Relationship to Adverse Event Categories

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

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

10.2 Serious Adverse Events

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

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

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

The reporting period for SAEs begins after informed consent is obtained and continues through 4 weeks after the last visit.

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

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

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

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

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

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

10.3 Safety Blood Collection

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

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

10.4 Pregnancy

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

10.5 Urgent Safety Measures

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

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

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

10.6 Medical Monitor Contact Information

Contact information and additional requirements will be provided in the MuSK-002 Study Reference Manual.

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

Gary Ingenito, MD, PhD
Chief Medical Officer
Catalyst Pharmaceuticals, Inc.
Tel: +1 305-420-3223

Email: gingenito@catalystpharma.com

11 APPROPRIATENESS OF MEASUREMENTS

The measures of safety used in this study are routine clinical and laboratory procedures.

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

12 STUDY PROCEDURES

12.1 Screening Visit

An ICF must be signed and dated by the patient, the Investigator or designee, and witness (if required) before any study-related procedures are performed. Refer to Section 9.4 for prohibited medications.

After patients have signed an ICF, they will be screened for enrollment into the study. The study activities listed below will be performed during the 14 days that constitute the Screening visit.

- Informed Consent;
- Inclusion/Exclusion criteria;
- Demographics (sex, race, ethnic origin, age);
- Medical history, including allergy history;
- Standard resting 12-lead ECG;
- Complete physical examination including weight and height;
- Vital signs (seated position), including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiration, and body temperature;
- Clinical laboratory tests including hematology, chemistry, and urinalysis;
- Serum pregnancy test in females of childbearing potential only;
- MuSK and/or AChR antibody testing (if not previously done and report available);
- EMG (if not previously done and report available);
- MG-ADL assessment;
- QMG score;
- SAEs; and
- Concomitant medications.

12.2 Open-label Run-in

Amifampridine dose will be titrated upward every 3 to 4 days, starting at 10 or 15 mg/day, at the discretion of the Investigator. Patients will either visit or have telephone/video contact with the site for each dose titration and at least one in-person site assessment at Week 3 of the run-in period (Table 1). When the Investigator determines that the patient has reached the maximal tolerable and efficacious dose, the patient should demonstrate they can remain on a stable dose and frequency for at least an additional 7 days. The Open-label Run-in period may be extended if additional time is needed for dose titration. At the end of this period, patients must show a ≥2-point improvement in MG-ADL from start of Run-in, to be eligible for randomization (Day 0).

Patients should be given a Drug Dosing Diary to record each dose of their open-label medication and instructions on how to complete the form.

Additional visits are allowed as necessary. Screening visit and start of Run-in (Day 1) may be combined into a single visit.

12.3 Period 1

12.3.1 Day 0

Patients who are deemed eligible for continuation will have the assessments/procedures listed below completed on Day 0 after taking a supervised dose of their medication for that day during the clinic visit, so that the assessments can occur in the prescribed relation to the time of medication administration.

- Confirmation of Inclusion/Exclusion criteria;
- Assessment of AEs/SAEs;
- Complete physical exam with weight;
- Vital signs (seated position), including SBP, DBP, heart rate, respiration, and body temperature;
- Standard resting 12-lead ECG;
- Clinical laboratory tests including hematology, chemistry, and urinalysis;
- Urine pregnancy test in females of childbearing potential only;
- Concomitant medications;
- Collect patient Drug Dosing Diary and perform IP accountability of open-label medication;

- Efficacy assessments following in-clinic dose of open-label medication, including:
  - MG-ADL;
  - QMG score.

Order of Assessment at Each Study Visit (when applicable)	Start Time After Dose (+ 10 minutes unless otherwise specified)
MG-ADL	45 minutes
QMG	After MG-ADL

All open-label IP should be collected from the patient. The pharmacy representative will dispense bottles containing amifampridine or placebo tablets, depending on the patient's randomization assignment, for daily outpatient administration for 10 days (Days 1-10), **starting after completion of all assessments on Day 0**.

Patients should be given a Drug Dosing Diary to record each dose of their double-blind medication and instructions on how to complete the form.

Patients continue administration of blinded study medication (amifampridine or placebo) until the Day 10 visit.

12.3.2 Period 1, Day 10 (or Early Termination Visit)

Patients will report to the study site on Day 10 (+1 day) and have the assessments/procedures listed below completed. Study personnel will administer a dose of the patient's blinded medication at the clinic on Day 10, so assessments can be performed according to the specified times in relation to the time of dose administration. The medication administered by study personnel should be the same as what the patient has been taking for the last 10 days. If the patient is taking study medication 3 or 4 times a day, the visit needs to be arranged such that one of the doses is administered by the study site personnel.

- Assessment of AEs/SAEs;
- Complete physical exam with weight;
- Vital signs (seated position), including SBP, DBP, heart rate, respiration, and body temperature;
- Urine pregnancy test in females of childbearing potential only;

- Urine drug screen;
- Concomitant medications;
- Collect patient Drug Dosing Diary and perform IP accountability;
- Efficacy assessments following in-clinic dose of double-blind medication, including:
  - MG-ADL;
  - QMG score.

Order of Assessment at Each Study Visit (when applicable)	Start Time After Dose (+ 10 minutes unless otherwise specified)
MG-ADL	45 minutes
QMG	After MG-ADL

13 DATA QUALITY ASSURANCE

Catalyst personnel or designees will visit the study site before initiation of the study to review with the site personnel information about the IP, protocol and other regulatory document requirements, any applicable randomization procedures, source document requirements, CRFs, monitoring requirements, and procedures for reporting AEs/SAEs.

At visits during and after the study, a CRA will monitor the site for compliance with regulatory documentation, with a focus on accurate and complete recording of data on CRFs from source documents, adherence to protocol, randomization (if applicable), AE/SAE reporting, and drug accountability records. A separate unblinded CRA may verify records at the site pharmacy.

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

14.1.1 Interim Analyses

No interim analyses are planned.

14.2 Analysis Populations

The following analysis populations will be defined for the study:

- Safety Population – The safety population will consist of all subjects who are enrolled in the study and have received at least one dose of amifampridine. (Subjects who begin the run-in period belong to the Safety Population whether they are randomized to a treatment or not.)
- Full Analysis Set (FAS): This population consists of all randomized subjects who receive at least 1 dose of IP (amifampridine or placebo) and have at least one post-treatment efficacy assessment. Subjects will be compared for efficacy according to the treatment to which they were randomized, regardless of the treatment actually received.
- Per Protocol (PP): This population is a subset of the FAS population, excluding subjects with major protocol deviations. The PP population will include all FAS subjects who:
    - Have no major protocol deviations or inclusion/exclusion criteria deviations that might potentially affect efficacy, and
    - Subjects who took at least 80% of the required treatment doses.
    - The PP population will be determined before database lock and unblinding subject treatment codes.

The FAS population will be the primary analysis set for all effectiveness analyses. The safety population will be used for the analysis of all safety variables and baseline characteristics. The PP population will be used for selected effectiveness analyses.

Subgroup analyses for efficacy and safety will be performed independently on the MuSK-MG and AChR-MG groups. No pooled analyses are planned.

14.3 Primary Endpoint(s)

The primary efficacy endpoint of the study is the change in MG-ADL score from Day 0 (baseline) for MuSK-MG subjects treated with amifampridine and placebo.

14.4 Secondary Endpoints

The secondary efficacy endpoints of the study are:

- The change in QMG score from Day 0 (baseline) for MuSK-MG subjects treated with amifampridine and placebo.
- The proportion of subjects with a change of 2, or more, in MG-ADL score for MuSK-MG subject treated with amifampridine and placebo.
- The proportion of subjects with a change of 3, or more, in QMG score for MuSK-MG subjects treated with amifampridine and placebo.

14.5 Safety Analysis

Prior to analysis, all AEs will be coded using the MedDRA coding dictionary. Based on these coded terms, TEAEs and SAEs will be summarized using system organ class and preferred terms, as well as by relationship to treatment. All AEs will be listed, regardless of whether they were study treatment related.

Vital signs will be summarized using descriptive statistics (mean, standard deviation, median, minimum, maximum, and number of non-missing observations) by time point. Changes from baseline will also be summarized by post-dose time point.

Clinical laboratory parameters will be summarized using descriptive statistics (mean, standard deviation, median, minimum, maximum, and number of non-missing observations) by time point. Changes from baseline will also be summarized by post-dose time point. In addition, a shift table will be constructed to show the shifts in laboratory results by parameter relative to the normal ranges. The number and percentage of subjects with the following shifts will be presented: normal/normal, normal/low, normal/high, low/low, low/normal, low/high, high/low, high/normal, and high/high. Similar shift tables will also be constructed for physical exam results. ECG results will be summarized in a shift table with the following shifts presented: normal/normal, normal/abnormal, abnormal/normal and abnormal/abnormal. A table of descriptive statistics for QTc time by treatment and time period will be created.

Additional safety analyses may be performed as described in the SAP for the study.

14.6 Efficacy Analysis

14.6.1 Primary Efficacy Endpoint Analyses

The MuSK-MG subgroup primary endpoint will be analyzed as the change in MG-ADL from baseline (Day 0) using the Wilcoxon-Mann-Whitney Rank sum test at a two-sided α of 0.050 using the FAS population. Descriptive statistics by treatment for the MG-ADL score for Day 0, Day 10, and change from Day 0 (baseline) will be presented.

14.6.2 Secondary Efficacy Endpoint Analyses

A number of secondary endpoints will be analyzed as described below and in the order presented below.

The first secondary endpoint of the MuSK-MG subgroup endpoint will be analyzed as the change in QMG from baseline (Day 0) using the Mann-Whitney-Wilcoxon Rank sum test at a two-sided α of 0.05 using the FAS population. Descriptive statistics by treatment for the QMG score for Day 0, Day 10, and change from Day 0 (baseline) will be presented.

The next secondary endpoints of the proportion of subjects in the MuSK-MG subject group with a change of 2, or more, in MG-ADL score followed by the proportion of subjects with a change of 3, or more, in the QMG score will be analyzed by Fischer's exact test at a two-sided α of 0.050 and using the FAS subject population. Totals for the proportions for each outcome, by treatment for these endpoints for change from Day 0 (baseline) will be presented.

The same statistical analyses, and in the order presented above for the primary and secondary analyses, will be conducted for the per protocol (PP) subject population. However, if the FAS and PP populations are the same, the PP analyses will not be done and the case study report will indicate that the FAS and PP populations are the same duplicate analyses were not needed and were not done.

14.7 Determination of Sample Size

The study is powered with respect to the primary endpoint of change in MG-ADL score from baseline for the MuSK-MG group of subjects. The study has approximately 60% power to detect a 2 point difference between amifampridine and placebo treatment groups for the change in MG-ADL from baseline (day 0). AChR-MG subjects are not expected to be respond robustly and positively and therefore no attempt will be made to adequately power the study for this group of study subjects.

14.8 Changes in the Conduct of the Study or Planned Analyses

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

Except for minor administrative or typographical changes, the IRB/IEC/REB must review and approve all protocol amendments. Protocol amendments that influence patient risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC/REB prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the ICF will be amended and approved by Catalyst and the IRB/IEC/REB, and all active patients must again provide informed consent.

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

15 COMPENSATION, INSURANCE, AND INDEMNITY

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

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

16 CASE REPORT FORMS AND SOURCE DOCUMENTS

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

Electronic case report forms (eCRFs) will be provided. The eCRF system, and procedures, and electronic signatures follow ICH requirements and applicable laws and local regulations.

All system users will be trained on the eCRF before being granted system access. In the event of an entry error, or if new information becomes available, users will correct the value by deselecting the erroneous response and then selecting or entering the factual response. The documented audit trail will include the reason for the change, the original value, the new value, the time of the correction and the identity of the operator.

In the application, study data on the eCRFs will be verified to the source data, which necessitates access to all original recordings, laboratory reports, and patient records. In addition, all source data should be attributable (signed and dated). The Investigator must therefore agree to allow direct access to all source data. Patients must also allow access to their medical records, and patients will be informed of this and will confirm their agreement when giving informed consent. The Investigator must review and electronically sign the completed eCRF casebook to verify its accuracy. A CRA designated by Catalyst will compare the eCRFs in the application with the original source documents at the study site and evaluate them for completeness and accuracy before designating them as “Source Data Verified” in the application. If an error is discovered at any time or a clarification is needed, the Data Manager, CRA, or designee, will create an electronic query on the associated field. Site personnel will then answer the query by either correcting the data or responding to the query. The Data Manager or CRA will then review the response and determine either to close the query or re–query the site if the response does not fully address the question. This process will be repeated until all open queries are answered and closed.

The CRO’s data management department may receive electronic transfers of laboratory data from the site’s local laboratory as well as other data from third-party vendors as appropriate.

The Investigator will then electronically sign the casebook, specifying that the information on the eCRFs is accurate and complete. An electronic copy of each site’s casebooks will be sent to each site for retention with other study documents.

17 STUDY MONITORING AND AUDITING

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

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

18 RETENTION OF RECORDS

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

All study records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until (1) there are no pending or contemplated marketing applications in an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The Investigator/institution should retain patient identifiers and records for at least 15 years after the completion or discontinuation of the study. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice. These documents should be retained

for a longer period, however, if required by the applicable regulatory requirements or by a Catalyst agreement. Catalyst must be notified and will assist with retention should Investigator/institution be unable to continue maintenance of patient files. It is the responsibility of Catalyst to inform the Investigator /institution as to when these documents no longer need to be retained.

19 USE OF INFORMATION AND PUBLICATION

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

20 REFERENCES

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21 INVESTIGATOR RESPONSIBILITIES

21.1 Conduct of Study and Protection of Human Patients

The Investigator will ensure that:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in compliance with ICH E6 (Section 4.8), and other applicable local regulations, are met.
- He or she will report to the sponsor adverse experiences that occur during the investigation in compliance with the standard operating procedures and policies of the IRB/IEC/REB and with applicable regulatory requirements.
- He or she has read and understands the information in the Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments.
- He or she will ensure that adequate and accurate records are kept in accordance with ICH and GCP requirements and to ensure those records are available for inspection.
- He or she will ensure that the IRB/IEC/REB complies with ICH and GCP requirements, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.
- He or she agrees to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent ICH and GCP requirements.
- He or she agrees to comply with electronic signature requirements in accordance with ICH requirements and applicable laws and local regulations.

22 SIGNATURE PAGE

Protocol Title:

A Randomized, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Amifampridine Phosphate in Patients with MuSK Antibody Positive Myasthenia Gravis, and a Sample of AChR Antibody Positive Myasthenia Gravis Patients

Protocol Number: MSK-002

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

Investigator Signature Date

Printed name: _____

Accepted for Catalyst:

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

Medical Monitor Signature Date

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

APPENDIX 1: MYASTHENIA GRAVIS-SPECIFIC ACTIVITIES OF DAILY LIVING (MG-ADL)

The MG-ADL is a self-report scale designed to assess the patient's MG symptoms and functional performance of activities of daily living. Eight items as listed below will be assessed by the patient at the protocol specified time points (see Table 1).

					Score
Grade	0	1	2	3	(0, 1, 2, 3)
1.Talking	Normal	Intermittent slurring of nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3.Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
4.Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
6.Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Bothersome eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
					MG-ADL score
					(items 1-8)

APPENDIX 2: QUANTITATIVE MYASTHENIA GRAVIS (QMG)

The QMG assesses the patient's general body strength and fatigability. The QMG will be administered at the protocol specified time points (see Table 1) by the same evaluator throughout the study.

TEST ITEM	NONE	MILD	MODERATE	SEVERE	SCORE
GRADE	0	1	2	3	
Double vision (lateral gaze) Sec.	60	11-59	1-10	Spontaneous	
Ptosis (upward gaze) Sec.	60	11-59	1-10	Spontaneous	
Facial Muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
Swallowing 4 oz. Water (1/2 cup)	Normal	Minimal	coughing or	throat	
Speech following counting aloud from 1-50 (onset of dysarthria)	None at #50	Dysarthria at #30-49	Dysarthria at #10-29	Dysarthria at #9	
Right arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	
Left arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	
Forced vital capacity	>80%	65-79%	50-64%	<50%	
Right hand grip: male (Kg) : female	>45 >30	15-44 10-29	5-14 5-9	0-4 0-4	
Left hand grip: male (Kg) : female	>35 >25	15-34 10-24	5-14 5-9	0-4 0-4	
Head, lifted (45%, supine) Sec.	120	30-119	1-29	0	
Right leg outstretched (45-50%,supine) Sec.	100	31-99	1-30	0	
Left leg outstretched (45-50%,supine) Sec.	100	31-99	1-30	0	
TOTAL SCORE: _____					