Cover Page for Protocol

Sponsor name:	Catalyst Pharmaceuticals, Inc.
NCT number	03579966
Sponsor trial ID	MSK-003
Official title of study	Long Term Safety Study of Amifampridine Phosphate in Patients with MuSK Antibody Positive and AChR Antibody Positive Myasthenia Gravis Patients
Document date	12 Nov 2017, USA

CLINICAL STUDY PROTOCOL

Study Title:	Long Term Safety Study of Amifampridine Phosphate in Patients with MuSK Antibody Positive and AChR Antibody Positive Myasthenia Gravis Patients
Protocol Number:	MSK-003
Investigational Product:	Amifampridine phosphate (3,4-diaminopyridine phosphate)
IND/EUDRACT Number:	106263 / 2017-004777-14
Indication:	Musk Antibody Positive Myasthenia Gravis
External Support:	Catalyst Pharmaceuticals, Inc.
Development Phase:	Phase 3
Medical Officer:	Gary Ingenito, MD, PhD
Study Design:	Open Label
Dose:	30-80 mg total daily dose
Patient Population:	Patients with MuSK antibody positive Myasthenia Gravis and a sample of patients with AChR antibody positive Myasthenia Gravis
Date of Protocol:	12 November, 2017 – USA

PROCEDURES IN CASE OF AN EMERGENCY

Emergency Contact Information

Role in Study	Name	Contact Information
Medical Monitor	Gary Ingenito, MD, PhD Chief Medical Officer	Catalyst Pharmaceuticals, Inc. 355 Alhambra Circle, Suite 1250 Coral Gables, FL 33134 Tel: 305-420-3200, ext. 123 Email: gingenito@catalystpharma.com
Coordinating Investigator	Renato Mantegazza, MD	Director Department of Neuroimmunology and Neuromuscular Diseases Carlo Besta Neurological Institute Via Celoria 11-201332 Milan, Italy
Clinical Project Lead	Adriana Manari	Catalyst Pharmaceuticals, Inc. 355 Alhambra Circle, Suite 1250 Coral Gables, FL 33134 Tel: 305-420-3217 Email: amanari@catalystpharma.com
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Synopsis

TITLE OF STUDY: Long Term Safety Study of Amifampridine Phosphate in Patients with MuSK Antibody Positive and AChR Antibody Positive Myasthenia Gravis Patients
PROTOCOL NUMBER: MSK-003
STUDY SITES: Up to 20 sites in USA and Europe
PHASE OF DEVELOPMENT: Phase 3
STUDY RATIONALE: The purpose of this study is to evaluate the long-term safety and tolerability of amifampridine phosphate in patients with MuSK antibody positive and AChR antibody positive myasthenia gravis (MG) patients who completed Protocol MSK-002.
OBJECTIVES: **Primary** • To characterize the long-term safety and tolerability of amifampridine phosphate in patients with MG
Secondary • To assess the clinical efficacy of amifampridine phosphate over time in patients with MG based on change in Myasthenia Gravis Activities of Daily Living Score (MG-ADL)
STUDY DESIGN AND PLAN: This is a long-term extension study for patients who participated in Protocol MSK-002 where the efficacy and safety of amifampridine was evaluated, in patients diagnosed with MuSK-MG or AChR-MG. The planned duration of participation for each patient is at least 9 months (i.e. until amifampridine is approved by Regulatory Agencies for the treatment of MG or the development program is discontinued for this indication). All patients who have completed study MSK-002 and sign an informed consent may enroll in the long-term study. Those patients who demonstrated benefit after completing the dose titration period but failed to meet the randomization criteria on Day 0 of MSK-002 may also be eligible for this study. The evaluations for MSK-002 can serve as baseline for the Long-Term study, if available

The optimal dose and schedule for amifampridine from the end of the Run-in Period from Study MSK-002 will initially be used for each patient. The Investigator may adjust the dose of amifampridine during the course of this trial, in order to optimize neuromuscular benefit for the patient. Clinic visits for safety assessment and for evaluation of MG-ADL will be made at Months 3, 6, 9, 12, 15, and 21. Additional visits may occur at the discretion of the Investigator.

NUMBER OF PATIENTS PLANNED:

Up to about 60 MuSK-MG patients and 10 AChR-MG patients will be studied.

CRITERIA FOR INCLUSION AND EXCLUSION:

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

1. Participated in the MSK-002 study
2. 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.
3. Female patients of childbearing potential must have a negative pregnancy test (urine human chorionic gonadotropin [HCG] at the end of MSK-002 study); and must practice an effective, reliable contraceptive regimen during the study and for up to 30 days following discontinuation of treatment.
4. 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 met any of the exclusion criteria in the original protocol or those listed below are not eligible to participate in the study:

1. Epilepsy and currently on medication.
2. Clinically significant abnormalities in 12 lead ECG, in the opinion of the Investigator.
3. Breastfeeding or pregnant at Screening or planning to become pregnant at any time during the study.
4. Intolerable amifampridine-related side effects
5. Treatment with an investigational drug (other than amifampridine) or device while participating in this study.
6. 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.

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 will be provided by Catalyst Pharmaceuticals, Inc., 355 Alhambra Circle, Suite 1250, Coral Gables, Florida, 33134, United States.

REFERENCE THERAPY, DOSE, ROUTE, AND REGIMEN:

None

DURATION OF TREATMENT:

Amifampridine will be continued as long as patients benefit from the treatment until the drug is approved by Regulatory Agencies or until the development of the drug is discontinued for this indication.

CRITERIA FOR EVALUATION:

Safety (primary endpoint):

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 findings, and concomitant medications will also be evaluated.

Efficacy (secondary endpoint):

Efficacy will be assessed by change in MG-ADL score over time.

STATISTICAL METHODS:

Sample Size Determination

The study is not powered with respect to any endpoint, but is an observational study to assess long term safety and lack of tolerance to the effects of amifampridine on MG-ADL.

Safety Analysis

Safety analyses will be conducted on the safety population (i.e. all patients who receive at least 1 dose of amifampridine. 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 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.

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 all patients who receive at least 1 dose of amifampridine and have at least one post-treatment efficacy assessment. The efficacy analysis will be descriptive and will be presented on observed data only independently on the MuSK-MG and AChR-MG

groups. No pooled analyses are planned.

2 TABLE OF CONTENTS

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

Abs	Antibodies
ACh	Acetylcholine
AChR	Acetylcholine receptor
AChR-MG	Acetylcholine receptor Myasthenia Gravis
ADL	Activities of Daily Living
AE(s)	adverse event(s)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATU	Autorisations Temporaires d'Utilisation Normative
CMS	congenital myasthenia syndromes
CRA(s)	clinical research associate(s)
CRF	case report form
CRO	contract research organization
DBP	diastolic blood pressure
ECG(s)	electrocardiogram(s)
eCRF	electronic case report form
EFNS	European Federation of Neurological Societies
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
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
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
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
ng/mL	*nanograms per* milliliter
PI	Principal Investigator
PK	pharmacokinetic
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
SOPs	standard operating procedures
TEAE(s)	treatment emergent adverse event(s)
US	United States

Definition of Terms:

Investigational Product (IP):

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

4 ETHICS

4.1 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.

4.2 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 being performed.

4.3 Patient Information and Informed Consent

A properly written and executed ICF, in accordance with the Declaration of Helsinki, ICH E6 (Section 4.8), 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.

5 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, both remotely and with onsite visits, 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.

6 INTRODUCTION

Information on disease background, amifampridine, previously completed nonclinical and clinical studies of amifampridine, is described in the Introduction of MSK-002 and in the

Investigator's Brochure supplied by Catalyst (June 2017). Investigators are to review this document before initiating this study.

Amifampridine 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.

Mori et al. (2012) found that amifampridine improved neuromuscular transmission by predominantly increasing ACh release in the neuromuscular junction of in mice with MG induced by antibodies against muscle-specific kinase (MuSK). Furthermore, a mouse model of MuSK-MG, amifampridine significantly enhanced neuromuscular transmission after 1 week of treatment without exacerbating loss of endplate AChRs (Morsch et al. 2013).

Multiple studies were conducted to evaluate the cardiac safety, pharmacokinetics and toxicity profile in rats and dogs. Reproductive and developmental toxicity studies with amifampridine were also conducted in rats and rabbit as well a variety of in vitro and in vivo genotoxicity studies, and in vitro metabolism/transporter studies. The main nonclinical findings related to amifampridine were central and autonomic nervous system effects, the development of Schwannomas, and histologic changes in muscle tissues. Below is an abbreviated summary of the effectiveness of amifampridine in MuSK-MG and overall safety in other patient populations.

6.1 Effectiveness in MuSK-MG and Other Indications

Small studies have demonstrated the beneficial effects of amifampridine in patients with MuSK-MG in 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. In an Investigator-Sponsored MuSK-MG randomized, double-blind, placebo-controlled, cross-over study conducted in Italy, 7 MuSK-MG patients demonstrated statistically significantly higher functional performance in all validated assessment scales when they were administered amifampridine compared to placebo. Tolerability to amifampridine was excellent (unpublished data).

Results from the MSK-002 study will also be used to establish efficacy of amifampridine in MuSK-MG.

A review of the literature documents that amifampridine is a safe and effective treatment in multiple neurologic disorders and is recommended by the EFNS for first-line symptomatic treatment of patients with LEMS (Skeie, 2006; Skeie, 2010; Lindquist, 2011).

6.2 Safety of Amifampridine and Amifampridine Phosphate

Safety data collected from 1,454 patients or healthy volunteers in controlled study LMS-002 [(Lambert-Eaton myasthenic syndrome LEMS)], controlled and uncontrolled published studies of LEMS or other neurologic conditions, a 3-year safety surveillance study (ATU), and pharmacokinetic (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 congenital myasthenia syndromes (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 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 (LEMS or MG) experienced seizures on a daily dose of ≥90 mg/day. 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 and multiple sclerosis (MS) (n=1); 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). It is noteworthy 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.

6.3 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. To date, current data demonstrate that amifampridine phosphate has an acceptable tolerability profile with a positive risk-benefit in patients treated with amifampridine, but longer-term studies are needed in patients with MG.

6.4 Study Rationale

A considerable amount of clinical experience is available with amifampridine 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. The present long-term extension study will evaluate safety and tolerability of amifampridine on clinical laboratory test variables, ECGs, AEs, vital signs, physical examinations and the effects on MG-ADL score over several months in patients with MuSK or AchR-MG. This information is needed to demonstrate that the product is safe and provides continued benefit to patients with MG.

7 STUDY OBJECTIVES

7.1 Primary Objective

The primary objective of the study is:

- To evaluate the long-term safety and tolerability of amifampridine in patients with MuSK-MG; and with AChR-MG.

7.2 Secondary Objective

The secondary objective of the study is:

- To assess the effect of amifampridine phosphate on Myasthenia Gravis Activities of Daily Living Score (MG-ADL).

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This open label outpatient extension study is designed to evaluate the long-term safety, tolerability of amifampridine in patients diagnosed with MuSK-MG and AChR-MG. In addition, evaluation of the effects of amifampridine on the MG-ADL score will be made. The study will enroll those patients who have completed the MSK-002 study and after all final

evaluations for that study have been completed, or those who demonstrated benefit after completing the dose titration period but failed to meet the randomization criteria on Day 0 of MSK-002.

The duration of participation for each patient is expected to be at least 9 months as patients may continue in the study until amifampridine is approved by Regulatory Agencies or the clinical development of amifampridine is terminated for this indication. In addition to amifampridine, patients will continue to receive previous concomitant medications, as needed.

After a new informed consent is signed and inclusion / exclusion criteria for the current protocol are satisfied, eligible patients will be given the optimal dose and dosing schedule that was identified in the Run-in Period from Protocol MSK-002.

The findings from the physical exam (including vital signs, weight); 12-lead ECG; clinical laboratory test results (including pregnancy testing) and any ongoing adverse events will be used as the baseline for the Long-Term safety evaluation.

The only efficacy measurement is the MG-ADL which will be completed every 3 or 6 months. Safety and tolerability assessments will be made every 3 or 6 months or more frequently at the discretion of the Investigator. The study will continue until amifampridine is approved by Regulatory Agencies or until development of the product for this indication is halted. The Investigator may alter the dose and dosing frequency during the Long-Term Study as well as schedule additional clinic visits for any reason.

Patients will be seen in the clinic at the end of Months 3, 6, 9, 12, 15 and 21 as detailed in the Schedule of Assessments in Table 1 and Section 11. In between the 3-or 6-month visits, patients may also have telephone/video contact with the site, or unscheduled visits, if needed.

Any unused medication must be brought back to the clinic at each visit for drug accountability, and an additional supply will be dispensed.

Table 1 Schedule of Events

Study Assessment or Event	Screening and Enrollment*	Study Month ± 1 week						
		3	6	9	12	15	21	End of Study[g]
Informed consent [a]	x							
Inclusion/Exclusion Criteria	x							
Complete physical exam [b]	x	x	x	x	x	x	x	x
Vital signs	x	x	x	x	x	x	x	x
12-Lead ECG	x	x	x	x	x	x	x	x
Clinical laboratory tests [c]	x	x	x	x	x	x	x	x
Pregnancy test [d]	x	x	x	x	x	x	x	x
Amifampridine Treatment	x	x	x	x	x	x	x	
MG-ADL		x	x	x	x	x	x	x
Dispense IP [e]	x	x	x	x	x	x		
IP accountability		x	x	x	x	x	x	x
Adverse events/SAEs [f]	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x

[a] Informed consent must be obtained before any study procedures are performed.
[b] Complete physical examination includes evaluation of all major body systems, including weight at all visits (Section 9.6.6).
[c] Clinical laboratory tests include serum chemistry, hematology, and urinalysis.
[d] Urine pregnancy tests will be obtained from female patients of childbearing potential.
[e] Pharmacist will dispense sufficient amount of medication until the next clinic visit. All unused medication must be returned to the clinic for drug accountability.
[f] SAE reporting commences after informed consent is signed. Non-serious adverse event reporting commences after the first dose of study drug for the current Long-Term Study.
[g] End of Study or early termination visit if the last visit does not coincide the scheduled 3- or 6-month visit.
*These data may be obtained from Study MSK-002. If data not available, then the assessment should be repeated.

8.2 Selection of Study Population

Patients who complete Protocol MSK-002 or who have demonstrated benefit after completing the dose titration period but failed to meet randomization criteria for MSK-002, and who meet the inclusion and exclusion criteria for participation in the current study will be eligible.

8.2.1 Inclusion Criteria

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

1. Participated in the MSK-002 study
2. 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.
3. Female patients of childbearing potential must have a negative pregnancy test (urine human chorionic gonadotropin [HCG] at the end of MSK-002 study); and must practice an effective, reliable contraceptive regimen during the study and for up to 30 days following discontinuation of treatment.
4. 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.

8.2.2 Exclusion Criteria

Individuals who met any of the exclusion criteria in the original protocol or those listed below are not eligible to participate in the study:

1. Epilepsy and currently on medication.
2. Clinically significant abnormalities in 12 lead ECG, in the opinion of the Investigator.
3. Breastfeeding or pregnant at Screening or planning to become pregnant at any time during the study.
4. Intolerable amifampridine-related side effects
5. Treatment with an investigational drug (other than amifampridine) or device while participating in this study.
6. 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.

8.2.3 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 9.4 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.

8.2.4 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.

8.3 Treatments

8.3.1 Treatments Administered

Catalyst or its designee will provide the study site with a supply of Investigational product: amifampridine tablets 10 mg at various intervals sufficient for the completion of the study.

Amifampridine 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.

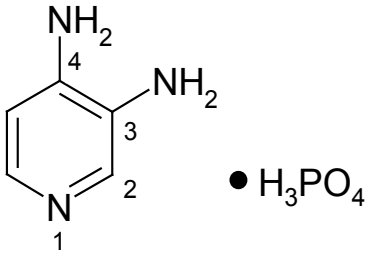
8.3.2 Identity of Investigational Product

The chemical name of amifampridine phosphate is:

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

The chemical structure is provided in **Error! Reference source not found.**.

Figure 1. Chemical Structure of Amifampridine Phosphate



8.3.2.1 Product Characteristics and Labeling

Drug product is formulated as a phosphate salt of amifampridine. Tablets were developed to provide the equivalent of 10 mg of amifampridine base for oral administration. Each tablet

contains amifampridine phosphate, microcrystalline cellulose, colloidal anhydrous silica, and calcium stearate. The bottles of tablets are labeled "Amifampridine Phosphate Tablets, 10 mg."

The tablets are to be dispensed by the pharmacy representative into suitably sized pharmacy containers for patient use. 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. Regional label requirements and translations should be used in accordance with local regulations.

8.3.2.2 Storage

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

8.3.3 Directions for Administration

All doses of study drug will be taken as outpatients. Test medication should be taken every day at approximately the same time, at the dose and frequency instructed by Investigator.

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 determined from the Run-in Period from MSK-002 or may be modified as the discretion of the Investigator. The maximum single dose is 20 mg.

8.3.4 Method of Assigning Patients to Treatment Groups

All patients will receive open label amifampridine. Details on study drug preparation, dispensing medication will be included in the Pharmacy Manual.

8.3.5 Selection of Doses Used in the Study

Initially, the daily amifampridine dose will be the one that was determined at the end of the Run-in Period from MSK-002. The usual 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.

8.3.6 Blinding

This is an open label study

8.3.7 Treatment Compliance

Patients will be instructed to take study medication as directed and bring 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.

8.3.8 Investigational Product Accountability

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

8.3.9 Return and Disposition of Clinical Supplies

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

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.

8.4 Prior and Concomitant Medications

All prescription and over-the-counter medications and herbal and nutritional supplements taken during the Long-Term study will be recorded on the designated CRF.

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 that should be used with caution in this study are those that prolong QTc interval.

8.5 Dietary or Other Protocol Restrictions

8.5.1 Dietary Restrictions

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

8.5.2 Contraception

Sexually active males and females of childbearing potential 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.

8.6 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 1Table 1** and in Section 11.

8.6.1 Adverse Events

The determination, evaluation and reporting of AEs will be performed as outlined in Section 9.

8.6.2 Vital Signs

Specific visits for obtaining vital signs are provided in Table 1 **Schedule of Events**and in Section 11. Vital signs will be measured while in a sitting position, after resting for 5 minutes, and include SBP and DBP measured in millimeters of mercury (mmHg), heart rate in beats per minute, respiration rate in breaths per minute. Weight (kg) and temperature in degrees C will also be measured. Clinically significant changes from baseline will be recorded as AEs.

8.6.3 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 **Error! Reference source not found.**. In brief, clinical laboratory evaluations are to be performed every 3 to 6 months. These tests can be performed more frequently at the discretion of the Investigator.

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 2 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	Pregnancy test, if applicable

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

8.6.4 Pregnancy Testing

Female patients of childbearing potential will have a urine pregnancy test at the end of the double blind period on Day 10 and at other time points specified in the Schedule of Events (Error! Reference source not found.) and in Section 11. Female patients with a positive pregnancy test at end of the double-blind study are not eligible for enrollment. Additional pregnancy tests will be performed at any visit in which pregnancy status is in question.

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

8.6.5 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 11. Clinically significant changes from baseline will be recorded as AEs.

8.6.6 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

Body weight will be measured with each physical examination throughout the study.

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

8.7 Efficacy Variable

Every 3 or 6 months, each patient will be assessed with the MG-ADL questionnaire.

8.7.1 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 30 days.

9 REPORTING ADVERSE EVENTS

9.1 Adverse Events

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

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

All non-serious AEs, even those which began under Protocol MSK-002, will be reported from the end of the double-blind study (MSK-002) through the termination visit or at the early termination visit and will be recorded on the AE page of the eCRF. All SAEs will be reported. The criteria for determining, and the reporting of SAEs is provided in Section 9.2.

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

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

The Investigator will determine the severity of each AE using grades defined in Table 1 Categories of Severity of Adverse Events(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 1 Categories of Severity of 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 2 Description of Relationship to Adverse Event Categories

Table 2 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.

9.2 Serious Adverse Events

A serious adverse event 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 for the current MSK-003 study 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.

9.3 Safety Blood Collection

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

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

9.4 Pregnancy

Pregnancy in a patient or partner should be reported within 24 hours of the site becoming aware of the pregnancy by fax or email of the Pregnancy 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.

9.5 Urgent Safety Measures

The regulations governing clinical trials state that the sponsor and Investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC, "…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.

9.6 Medical Monitor Contact Information

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

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

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

Email: gingenito@catalystpharma.com

10 APPROPRIATENESS OF MEASUREMENTS

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

The efficacy measure is a self-report on how the patient is functioning for activities of daily living. This standardized test has been previously used for determination of response to therapeutic intervention in patients with MG.

11 STUDY PROCEDURES

11.1 Start of Long Term Study

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

The following procedures are to be performed as schedule for either the Day 0 (in the case where patient was not randomized) or the Day 10 visit for the MSK-002 protocol and can

serve as baseline for the Long-Term study. Any procedure not performed for MSK-002 protocol needs to be completed for this trial.

- Informed Consent for MSK-003;
- Inclusion/Exclusion criteria for the current study must be verified;
- Standard 12-lead ECG after 5 minutes in the supine position;
- Complete physical examination including weight;
- Vital signs (seated position), including SBP, DBP, heart rate, respiration, and body temperature;
- Clinical laboratory tests including hematology, chemistry, and urinalysis;
- Urine pregnancy test in females of childbearing potential only;
- MG-ADL (use data from Day 0 of MSK-002 for all patients);
- AEs;
- Concomitant medications.

11.2 End of Months 3, 6, 9, 12, 15 and 21 in Long Term Study

The following assessments and procedures will be determined at the end of Months 3, 6, 9, 12, 15 and 21. Each month has a clinic visit window of ± 1 week. Additional visits are allowed as necessary.

- Assessment of AEs/SAEs;
- Complete physical exam with weight;
- Vital signs (seated position), including SBP, DBP, heart rate, respiration, and body temperature;
- Standard 12-lead ECG after 5 minutes in the supine position;
- Clinical laboratory tests including hematology, chemistry, and urinalysis;
- Urine pregnancy test in females of childbearing potential only;
- Concomitant medications;
- IP accountability of medication;
- MG-ADL

All IP should be collected from the patient at each visit, in order to perform drug accountability. The site will dispense sufficient amifampridine for daily outpatient

administration for 90 days (or 180 days from Months 15 to 21). If the Investigator wants to evaluate the patient more frequently, fewer tablets can be dispensed.

Patients may continue to receive amifampridine until the study is terminated, the patient decides to withdraw from the study, or the development program is discontinued for this indication.

11.2.1 End of Study Visit

Patients will report to the study site at the end of the study and have the assessments and procedures listed below completed. This visit may be incorporated at the scheduled 3-or 6-month visit.

- Assessment of AEs/SAEs;
- Complete physical exam with weight;
- Vital signs (seated position), including SBP, DBP, heart rate, respiration, and body temperature;
- 12-Lead ECG;
- Clinical laboratory tests;
- Urine pregnancy test in females of childbearing potential only;
- Concomitant medications;
- IP accountability;
- MG-ADL

12 DATA QUALITY ASSURANCE

Catalyst personnel or designees will visit or telephone the study site before initiation of the study to review with the site personnel information about the IP, protocol and other regulatory document requirements, 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, AE/SAE reporting, and drug accountability records. The CRA will also verify records at the site pharmacy.

13 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

13.1 Statistical and Analytical Plans

13.1.1 Interim Analyses

No interim analyses are planned.

13.2 Analysis Populations

The analysis population in this study is the safety population and will consist of all patients who are enrolled in the Long-Term study and have received at least one dose of amifampridine. Safety evaluation from MuSK-MG and AChR-MG groups will analyzed separately.

13.3 Primary Endpoint

The primary endpoint of the study is safety and tolerability of amifampridine at Months 3, 6, 9, 12, 15 and 21. For more details see Section 13.5 below.

13.4 Secondary Endpoint

The secondary endpoint of the study is the MG-ADL score at Months 3, 6, 9, 12, 15 and 21.

13.5 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 will be created.

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

13.6 Determination of Sample Size

This is an observational study and no hypothesis is being tested. Collection of long term safety and MG-ADL scores are required to demonstrate that amifampridine is safe and well tolerated in the MG population and if there is a change in dose requirements with time.

13.7 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.

14 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.

15 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.

16 STUDY MONITORING AND AUDITING

Qualified individuals approved and/or designated by Catalyst will monitor all aspects of the study according to GCP and SOPs for compliance with applicable government regulations. The monitoring will take place on site as well as remotely as the monitors can view all clinical data electronically and can follow-up with any queries for more information. 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.

17 RETENTION OF RECORDS

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

All study records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until (1) there are no pending or contemplated marketing applications in an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The Investigator/institution should retain patient identifiers 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.

18 USE OF INFORMATION AND PUBLICATION

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

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20 INVESTIGATOR RESPONSIBILITIES

20.1 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.

2 SIGNATURE PAGE

Protocol Title:

Long Term Safety Study of Amifampridine Phosphate in Patients with MuSK Antibody Positive and AChR Myasthenia Gravis Antibody Positive Myasthenia Gravis Patients

Protocol Number: MSK-003

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

Investigator Signature Date

Printed name: _____

Accepted for Catalyst:

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

Gary Ingenito for 18 May 2018

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 **Error! Reference source not found.**

					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)