CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized, Outpatient Two-period Two-treatment Crossover Study to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with Congenital Myasthenic Syndromes (CMS)
Protocol Number:	CMS-001
Investigational Product:	Amifampridine phosphate (3,4-diaminopyridine phosphate)
IND/EUDRACT Number:	106263 / 2010-021850-20
Indication:	Congenital Myasthenic Syndromes (CMS)
Sponsor:	Catalyst Pharmaceuticals, Inc.
Development Phase:	Phase 3
Medical Officer:	Gary Ingenito, MD, PhD
Study Design:	Double-blind, Placebo-controlled, Randomized, Outpatient Two-period Two-treatment Crossover
Dose:	10-80 mg total daily dose or placebo equivalent
Patient Population:	Patients with CMS
Date of Protocol:	15 September, 2015 (FINAL)
Date of Amendment 1:	2 February 2016
Date of Amendment 2:	7 March 2016
Date of Amendment 3:	7 July 2016
Date of Amendment 4:	25 April 2017
Date of Amendment 5:	26 June 2017

2 PROCEDURES IN CASE OF AN EMERGENCY

Table 1. Emergency Contact Information

Role in Study	Name	Contact Information
Medical Monitor	Gary Ingenito, MD, PhD, Chief Medical Officer	Catalyst Pharmaceuticals, Inc. 355 Alhambra Circle, Suite 1250 Coral Gables, FL 33134 Tel: +1 305-420-3200, ext. 123 Email: gingenito@catalystpharma.com
Clinical Project Lead	Sumit Verma MD	Assistant Professor of Pediatrics and Neurology, Emory Univeristy School of Medicine, Atlanta, GA Staff Pediatric Neurologist, Children's Healthcare of Atlanta 1001 Johnson Ferry Road, Atlanta, GA
SAE Reporting	Reported within 24 hours	24-hour safety hotline: 305-420-3233 To ensure notification in real time, also email reports to: jrubine@catalystpharma.com and gingenito@catalystpharma.com

3 SYNOPSIS

NAME OF COMPANY:
Catalyst Pharmaceuticals, Inc.
355 Alhambra Circle, Suite 1250
Coral Gables, FL 33134

NAME OF FINISHED PRODUCT:
Firdapse®

NAME OF INVESTIGATIONAL PRODUCT:
amifampridine phosphate (3,4-diaminopyridine phosphate)

TITLE OF STUDY:
A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized, Outpatient Two-period Two-treatment Crossover Study to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with certain Congenital Myasthenic Syndromes (CMS) amenable to treatment.

PROTOCOL NUMBER:
CMS-001

STUDY SITE:
Multicenter at up to 5 sites in the United States and 3 sites in Canada

PHASE OF DEVELOPMENT:
Phase 3

OBJECTIVES:

- To characterize the overall safety and tolerability of amifampridine phosphate compared with placebo in patients with CMS; and
- To assess the clinical efficacy of amifampridine phosphate compared with placebo in patients with CMS, based on improvement in subject global impression (SGI) and motor function measure (MFM 20 or 32) scores.

STUDY DESIGN AND PLAN:
This randomized (1:1), double-blind, placebo-controlled, outpatient two-period, two-treatment crossover study is designed to evaluate the efficacy and safety of amifampridine phosphate in patients diagnosed with certain genetic subtypes of CMS and demonstrated open label (amifampridine phosphate) or history of sustained amifampridine benefit from treatment. After a period of unblinded drug escalation/treatment, blinded treatment effect will be assessed in a randomized fashion of continuation or cessation of drug, each blinded treatment period separated by a stabilization period. The study is planned to include up to 23 male and female patients. The planned duration of participation for each patient is approximately 56 days, excluding the screening period, which can last up to 14 days.

All patients will be screened for eligibility to participate in the study. Those successfully completing screening will have procedures/assessments (see Table 3) completed on Day 1 of the run-in period. Patients who are previously naïve to amifampridine (3,4-DAP) or amifampridine phosphate treatment will then begin open-label up-titration of medication, with frequent clinic visits/telephone evaluation for up to 4 weeks during run-in period, until stable dose and frequency of amifampridine phosphate is achieved for 7 days. At the end of the 7 days of stable dosing, there must be demonstrated efficacy as assessed by improvement on the MFM 20 or 32 in order for the patient to participate in the randomized two-period, two-treatment crossover portion of the study.

Patients on a stable dose of amifampridine phosphate with a history of meaningful improvement in motor function are eligible immediately for randomization. Those who are on a stable pre-trial dose of 3,4-DAP will be transitioned to equivalent dose of amifampridine phosphate for 7 days. At this point (labeled Day 0) the patient will be randomized to a Treatment Sequence and undergo procedures/assessments (Table 3). Study medication at the stable dose or placebo, will be dispensed by the site pharmacist, according to the randomization schedule, beginning with the dose following completion of assessments on Day 0 and for the 8 day Period 1. Following experimental Period 1, patients will be returned to the stable dose administered at the end of the open-label run-in period from days 9-21, followed by Period 2 dosing for 8 days (Days 22-29). Patients who were on a stable does of amifampriding phosphate with history of meaningful improvement prior to randomization in CMS-001, will be returned to the same stable dose from days 9-21, followed by Period 2 dosing for 8 days (Days 22-29).

After completion of Period 2, patients will be eligible for expanded access with restoration of open-label amifampridine phosphate at the same dose and frequency as established in the run-in phase of the study. Patients who were on stable dose of amifampriding phosphate with history of meaningful improvement prior to randomization in CMS-001, will be returned to the same stable dose and frequency during their participation in the expanded access program.

Open-label Run-in

Patients who are naïve to amifampridine or amifampridine phosphate treatment are each potentially eligible, but the pathway to enrollment depends upon previous drug exposure and efficacy. For those naïve to either, amifampridine phosphate dose may be titrated upward every 3 to 4 days, per the dosing guidelines in Table 4, at the discretion of the investigator, for up to 4 weeks, including 1 week of stable dose and frequency before being randomized to a Treatment Sequence in Period 1. Measurements of clinical improvement will be administered at the outset and repeated as clinically indicated during the titration period, to assess open-label efficacy. Dosing can be increased or decreased by the investigator during the run-in phase. Enrollment and randomization for patients in this group of initially drug-naïve patients can only occur after achievement of stable dose for at least 7 days with demonstrated 20% or greater improvement in MFM 20 or 32 (depending on the age of patient) compared to Day 1 run-in assessment.

Patients already receiving 3,4-DAP or amifampridine phosphate treatment for CMS, and meeting the inclusion and exclusion criteria are eligible to participate in this study. The patient should report or investigator judges there is a history of improvement on 3,4-DAP or amifampridine phosphate treatment; improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants. They can be randomized into Period 1 if on stable dose and frequency of amifampridine phosphate for at least 1 week before being randomized to a Treatment Sequence.

Treatment Group A or B

Period 1 (Days 1-8) (+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 the last day of the run-in period (Day 0) to either Sequence 1 or 2 and commence Period 1 for the respective Treatment Sequence. Only after assessments are completed on Day 0, the patient will begin to receive either amifampridine phosphate tablets or placebo tablets for 8 days as an outpatient, with a dose of the same medication on the day of scheduled study visit (Day 8) in the clinic, in order to facilitate efficacy assessments, under double-blind conditions. If the patient is on a BID or TID regimen during Period 1, the Day 8 assessments should occur after the same dose that corresponds to when assessments were done on Day 0. Any unused portion of double-blind dispensed drug will be returned to the site before dispensing drug for the Re-Stabilization Period.

Re-Stabilization Period (Days 9-21) (+1 day)

Patients will be administered amifampridine phosphate at the same dose and frequency established as the stable dose in the open-label run-in phase for a 14-day period, under open-label conditions.

Patients who were on stable dose of amifampriding phosphate with history of meaningful improvement prior to randomization in study CMS-001, will be returned to the same stable dose and frequency during the re-stabilization period.

Period 2 (Days 22-29) (+1 day)

After completion of Period 1 and the re-stabilization period, according to randomization sequence, patients will receive the blinded study medication/placebo for Period 2 for 8 days (Day 22 – 29) as an outpatient with a dose of the same medication on the day of scheduled study visit (Day 29) in the clinic, in order to facilitate efficacy assessments, under double-blind conditions. If the patient is on a BID or TID regimen during Period 2, the Day 29 assessments should occur after the same dose that corresponds to when assessments were done on Day 0. Any unused portion of double-blind dispensed drug will be returned to the site before enrolling the patient in the expanded access program and dispensing open-label drug.

During all phases of the study, safety and efficacy assessments will be performed as detailed in the Schedule of Assessments in Table 3 and Section 13.

NUMBER OF PATIENTS PLANNED:
Approximately 23 patients to enroll in the study.

CRITERIA FOR INCLUSION AND EXCLUSION:

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

1. Patient or parent 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, or the patient's legal guardian or caregiver with durable power of attorney can provide written informed consent. An assent form must also be signed if in the judgement of the IRB/IEC/REB the children are capable of providing assent.
2. Male or female age 2 years and above.
3. Body weight ≥10 kg.
4. Genetically-confirmed CMS involving acetylcholine receptor defect, Rapsyn deficiency, MuSK deficiency, Dok-7 deficiency, SYT2 mutations, SNAP25B deficiency, and fast channel syndrome.
5. In patients who are naïve to 3,4-DAP or amifampridine phosphate, MFM 20 or 32 score equal or less than 48 or 76, respectively, at Screening
6. In patients who are naïve to 3,4-DAP or amifampridine phosphate, improvement of >20% in MFM 20 or MFM 32 scores after open label period of uptitration of dose
7. In patients who are previously stabilized on 3,4-DAP or amifampridine phosphate, a history of meaningful improvement in motor function (in the opinion of the investigator).
8. Willingness of patients receiving pyridostigmine, albuterol, ephedrine, or fluoxetine to remain on a stable dose of these medications throughout the study interval.
9. Female patients of childbearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG] at Screening); and must practice effective, reliable contraceptive regimen during the study. Acceptable methods of contraception include hormonal contraception (i.e., birth control pills, injected hormones, dermal patch or vaginal ring), intrauterine device, barrier methods (diaphragm, condom) with spermicide, or surgical sterilization (tubal ligation).
10. 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.

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

1. CMS subtype diagnosis of acetylcholinesterase deficiency, slow-channel syndrome, LRP4 deficiency, and plectin deficiency.
2. Cardiac conduction defects on Screening electrocardiogram (ECG).
3. Seizure disorder.
4. Clinically significant abnormal laboratory values at Screening, in the opinion of the

investigator.

5. Pregnancy or breastfeeding at Screening or planning to become pregnant at any time during the study.
6. Any systemic bacterial or other infection, which is clinically significant in the opinion of the investigator and has not been treated with appropriate antibiotics.
7. Treatment with an investigational drug (other than 3,4-DAP or amifampridine phosphate), device, or biological agent within 30 days before Screening or while participating in this study.
8. Any other 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 confounds the assessment of the patient.
9. History of drug allergy to any pyridine-containing substances or any amifampridine phosphate excipient(s).

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

The investigational product (IP) is amifampridine phosphate tablets 10 mg, and it will be provided in round, white-scored tablets, containing amifampridine phosphate formulated to be the equivalent of 10 mg amifampridinebase per tablet. The total daily dose will be individually determined by the investigator, within the bounds of a total daily dose of 10 mg to 80 mg, divided into doses taken 2 to 4 times per day as prescribed by the investigator, based on optimal neuromuscular benefit.

Amifampridine phosphate tablets are to be taken orally by mouth with food throughout the study. Children unable to swallow tablets will have the tablets crushed and mixed with a small amount of food, and children with a nasogastric or gastrostomy tube will have the tablets crushed and diluted in 5 to 10 mL of water and given through the tube. Scored tablet can be split to obtain 5 mg dose, if required.

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

REFERENCE THERAPY, DOSE, ROUTE, AND REGIMEN:

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

DURATION OF TREATMENT:

Approximately 56 days (excluding up to 14-day screening period) after enrollment. The run-in phase requires that the patient must be on a stable dose and dose regimen for the last 7 days 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 phosphate versus placebo for:

- SGI;
- MFM 20 or 32 (MFM 20 (individual <7 years) and MFM 32 (individual ≥ 7 years));
- Clinical Global Impression-Severity (CGI-S); and
- Clinical Global Impression-Improvement (CGI-I).

Optional tests to be performed are;

- Stimulated single fiber electromyogram (SFEMG)
- "Slurp" test

STATISTICAL METHODS:

Sample Size Determination

Assuming a standardized between-treatment difference of 0.5, 23 patients per sequence will ensure power of 90% for the 2-sided test at the 0.05 level using the standard 2-by-2 crossover analysis.

Safety Analysis

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

Efficacy Analysis

Efficacy will be described for 2 datasets:

- Full Analysis Set (FAS): This population consists of all randomized patients who receive at least 1 dose of IP (amifampridine phosphate 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.

If the PP Population is the same as the FAS, then the results will be presented only for the FAS. Exclusion from the FAS and PP Population will be finalized prior to database lock and subsequent unblinding.

Summary statistics will be provided by treatment and period for CGI-I, CGI-S, Change From Baseline (CFB) for CGI-S, the optional Slurp Test, and variables associated with the optional SFEMG.

The analysis of CFB for SGI is the primary efficacy analysis and will be performed using the standard analysis for a 2-by-2 crossover design. Summary statistics for SGI and CFB for SGI will be presented by treatment and period. P-values <0.05 wil be considered statistically significant.

The total score for MFM and the subtotal for each of the three dimensions (Standing and transfer, Axial and proximal motor function, and Distal motor function) will be standardized by the possible maximum for both MFM 20 and MFM 32. The CFB for these standardized scores will be analyzed using the standard analysis for a 2-by-2 crossover design for MFM 20 and MFM 32 separately and pooled, with the latter being the secondary and the separate analyses being supportive. The total scores, subtotals for each dimension, and the corresponding standardized scores will be summarized by treatment and period for MFM 20 and MFM 32 separately and standardized scores will be summarized by treatment and period for MFM 20 and MFM 32 pooled. P-values <0.05 wil be considered statistically significant.

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5 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

3,4-DAP	3,4-diaminopyridine
ACh	acetylcholine
AChR	acetylcholine receptor
ADL	Activities of Daily Living
ADME	absorption, distribution, metabolism, and excretion
AE(s)	adverse event(s)
AIN	adult idiopathic nystagmus
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
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
Ca^{+}	calcium ion
CI	confidence interval
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
C_{max}	peak plasma concentration
CMG	congenital myasthenia gravis
CMS	congenital myasthenic syndromes
CNS	central nervous system
CRA(s)	clinical research associate(s)
CRF	case report form (paper or electronic)
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DBP	diastolic blood pressure
EC	European Commission
ECG(s)	electrocardiogram(s)
EFNS	European Federation of Neurological Societies
EMG	Electromyogram

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

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

Definition of Terms:

Investigational Product (IP):

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

6 ETHICS

6.1 Independent Ethics Committee

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

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

6.2 Ethical Conduct of Study

This study will be conducted in accordance with the following:

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

6.3 Patient Information and Informed Consent

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

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with Catalyst, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected

health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each patient. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the patient and the patient will be removed from the study.

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

7 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

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

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

Email: gingenito@catalystpharma.com

Clinical research associates (CRAs) or trained designees will monitor 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. Catalyst's Regulatory Affairs Department (or designee) will be responsible for the timely reporting of serious adverse events (SAEs) to appropriate regulatory authorities as required.

In multicenter studies, a Coordinating Investigator will be identified who will be responsible for study overview.

Laboratory evaluations will be performed at both central laboratories and the local laboratories associated with the study sites. Additional details will be provided in the CMS-001 Study Reference Manual.

8 INTRODUCTION

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

8.1 Disease Background

The neuromuscular junction (NMJ) is the specialized synapse between the motor nerve terminal and the muscle fiber. Defects in NMJ function present with variable and often fluctuant symptoms such as fatigue, muscle weakness, droopy eyelids, double vision, swallowing and breathing difficulties. NMJ disorders are both inherited and acquired in nature. Congenital myasthenic syndromes (CMS) are a group of heterogeneous inherited disorders caused by mutations in genes encoding proteins essential for the integrity of neuromuscular transmission. Most CMS are caused by molecular defects in the muscle nicotinic acetylcholine receptor, but they can also be caused by mutations in presynaptic proteins, mutation in proteins associated with the synaptic basal lamina, defects in endplate development and maintenance, or defects in protein glycosylation (Engel, 2007). More than 20 different genetic mutations at the presynaptic, synaptic, and postsynaptic level of neuromuscular junction have been described.

CMS is rare, estimated at one-tenth that of myasthenia gravis, which in itself is rare (estimated at 25 to 125 per million) (Eymard, 2013; Abicht, 2012). Worldwide, approximately 2,000 to 3,000 patients have been diagnosed on a molecular level (Schara, 2012). A recent report on genetically-confirmed CMS cases in the United Kingdom indicates a prevalence of 9.2 per million in children under 18 years of age, equally affecting girls and boys (Parr, 2014).

CMS is characterized by fatigable weakness of skeletal muscle (ocular, bulbar, limb muscles), with an onset typically at birth or early childhood, although rarely it can manifest in adolescence and adulthood (Abicht, 2012; Schara, 2012). Clinically, hypotonia is common, as are ophthalmoplegia and ptosis, dysphonia and swallowing disturbance, facial paresis, and progressive muscle weakness (Eymard, 2013; Abicht, 2012). The severity and clinical course of the disease are highly variable, reflective of the underlying genetic defect.

The diagnosis and management of children with CMS is challenging and response to treatment in CMS depends on the type of defect (pre-synaptic, synaptic, post-synaptic) and the kinetics of the channel affected (fast versus slow). Most patients are eligible and respond to pharmacologic intervention, including esterase inhibitors, 3,4-diaminopyridine (3,4-DAP),

ephedrine, fluoxetine or quinidine, and albuterol (Eymard, 2013; Abicht, 2012; Schara, 2012; Engel, 2007). The particular therapy is dictated by the diagnosed CMS subtype, as drugs beneficial in one subtype can be detrimental in another subtype.

8.2 Amifampridine

Amifampridine (3,4-DAP) is a non-specific voltage-dependent potassium (K^+) channel blocker used to treat many of the congenital myasthenic syndromes, particularly those with defects in choline acetyltransferase, downstream kinase 7, and those where any kind of defect causes "fast channel" behavior of the AChR. Its blockade of K^+ channels causes depolarization of the presynaptic membrane and slows down or inhibits the repolarization phase of an action potential. Prolongation of the action potential duration increased opening of pre-synaptic slow voltage-dependent calcium (Ca^{2+}) channels, increasing Ca^{2+} influx and consequent increase in synaptic vesicle exocytosis (quantal content) with each depolarization event, thus releasing an increased level of ACh into the synaptic cleft (Maddison, 1998a; Maddison, 1998b) The influx of ACh into the presynaptic cleft enhances neuromuscular transmission, providing improved muscle function in those cases of CMS where defects of diminished post-synaptic response are demonstrated or postulated.

Over the last 25 years, a considerable amount of clinical experience with amifampridine has been gained, which provides a strong body of evidence for its efficacy and safety in the treatment of patients with neurologic disorders, including MG, CMS, Lambert-Eaton myasthenic syndrome (LEMS), multiple sclerosis (MS), downbeat nystagmus, and amyotrophic lateral sclerosis (ALS). Amifampridine has been recommended as first-line symptomatic treatment for LEMS by the European Federation of Neurological Societies (EFNS) (Skeie, 2006; Skeie, 2010; Lindquist, 2011) and amifampridine tablets 10 mg (as amifampridine phosphate) (Firdapse® Tablets) is marketed for the treatment of LEMS in the European Union (including Norway and Iceland), Israel, and Switzerland. The collective body of data indicates that amifampridine/ amifampridine phosphate is well tolerated up to and including 80 mg/day (Firdapse Investigator Brochure, February 2015).

8.3 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 and 13-week) and dog (28-day and 9-month)
- Reproductive and developmental toxicity in rat and rabbit
- Six *in vitro* and *in vivo* genotoxicity studies

Safety factors based on data from the 4-week toxicity/TK studies in rat and dog, the 13-week toxicity/TK study in rats along with a PK study in fasted rats are presented in Table 2. Peak plasma concentration (C_{max}) values were used in calculating the exposure-based safety factors as the central nervous system (CNS) and autonomic nervous system (ANS) effects are correlated to plasma concentration levels. C_{max} data from the bioavailability/bioequivalence study in healthy volunteers were used to compare with animal C_{max} data. Human safety factors calculated using mean C_{max} from a PK study in fasted rats are 2.8 (male) and 7.8 (female). The safety factor based on average C_{max} in male and female dog versus human is 1.2 and 1.1, respectively.

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

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

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

[a] Based on a 60-kg human and a total daily dose of 80 mg/kg or 20 mg amifampridine phosphate, TID in order to calculate body surface area and C_{max} based safety factors, respectively.
[b] Dose was 24 mg/kg/day, TID in fasted rats; based on fasted first dose.
[c] Based on Day 27 of the first 4-week study in rat.
[d] Based on Day 92 after third daily dose.
[e] Based on Day 0 of the first 4-week study in dog.
[f] Bioavailability/Bioequivalent clinical study in fasted healthy volunteers.

The main nonclinical findings of CNS and ANS effects and histologic changes in muscle tissues after administration of amifampridine are in accordance with the mechanism of action. No new treatment-related findings in the nonclinical program have been observed that would limit the use of amifampridine at the planned clinical maximum daily oral dose of 60 mg (≤16 years of age) and 80 mg (>16 years of age) in this study involving patients with CMS.

8.4 Previous Clinical Studies

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

8.4.1 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; therefore, administration with food is recommended based on the current study.

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

8.4.2 Efficacy of Amifampridine in CMS

Efficacy of 3,4-DAP in patients with CMS has been reported in the published literature. Few clinical studies are reported, with most reports being case series or case reports. An open prospective trial conducted by Palace and colleagues (1991) reported improvement with oral 3,4-DAP in congenital myasthenia syndrome in 16 patients (8 males and 8 females) ranging in age from 7 to 47 years. All but 1 patient showed improvement in strength scores, and the group as a whole showed highly significant increase in muscle strength. Although this study included younger patients, only 2 patients were less than 10 years of age, and genetic etiology for congenital myasthenia was unknown with outcome measures largely dependent on patient cooperation and motivation. One death of 5-year-old girl with severe congenial myasthenia who developed fatal pneumonia after several weeks of 3,4-DAP, though not thought to have contributed to this event. Anlar and colleagues (1996) conducted a double-blinded, placebo-controlled, crossover study investigating the effects of 3,4-DAP in 11 patients (5-24 years of age) with either a diagnosis of congenital myasthenia gravis (CMG) or juvenile myasthenia gravis (JMS). None of the 5 JMS patients responded to 3,4-DAP treatment. Five of the 6 CMG patients showed clinical improvement, with placebo effect noted in 3 patients. The authors concluded that 3,4-DAP treatment may be beneficial in some CMG patients but may have different effects on various presynaptic and postsynaptic defects of neuromuscular transmission resulting in CMS.

With the advancements of whole-exome sequencing, approximately 20 CMS disease genes have been identified. Harper and Engel's open-label uncontrolled study (2000) was the first to look at patients with different mutation forms of CMS. With a total of 31 patients, this study showed all patients with fast-channel CMS had sustained improvement and about one-third of AChR deficiency patients had sustained improvement. A handful of case reports and case series has also shown the efficacy of 3,4-DAP in different mutation forms of CMS. Beeson and colleagues (2005) reported 19 patients with CMS who received 3,4-DAP (doses not specified), with 15 maintained on their existing anti-AChE medication. Good response to 3,4-DAP was observed in CMS due to mutations of the following genes: *MuSK* (n=1), *CHRNE* (n=4), *COLQ* (n=1), *RAPSN* (n=1), and unknown (n=6). For the patient with *COLQ*-CMS, a positive effect was found at 26 years of age, with a clear gain of axial and limb strength. In a single report (Mazell, 2015), use of 3,4-DAP in a 4-year-old girl with well-defined *CHRNE*-CMS showed promising results using stimulated jitter analysis and MFM score as outcome measures. In long-term follow-up of 15 *COLQ*-CMS patients ranging in age from 3 to 48 years (mean 19 years), all relapses ended spontaneously or with 3,4-DAP (30 to 60 mg daily) or ephedrine with no residual impairment (Wargon, 2012). Associated

respiratory crises were reported in 3 of the 8 patients. From a pediatric standpoint, this adverse event was significant as puberty was identified as a triggering factor in 6 of 8 patients.

Two children with *RAPSN*-CMS improved clinically with the addition of 3,4-DAP in conjunction with pyridostigmine (Banwell, 2004). Clinically, both children manifested with hypomotility *in utero*, fatigable ocular and limb weakness since birth, decreased strength during viral illness, decremental response on EMG, and absence of AChR antibodies. One child had a more severe clinical course with recurrent episodes of respiratory failure, contractures, and craniofacial malformations. The addition of 3,4-DAP in this 14-year-old boy led to increased endurance and a marked reduction in fatigable weakness. In the second child, a 9-year-old girl maintained on pyridostigmine since 4 months of age, experienced significant improvement in endurance after treatment with 3,4-DAP, allowing for increased activity (i.e. jump rope, run, participate in dance, ride a horse). In another report of 11 patients with *RAPSN*-CMS, addition of 3,4-DAP to the pyridostigmine regimen resulted in further clinical improvement (Milone, 2009).

Four reports have evaluated 3,4-DAP in *DOK-7*-CMS. Ben Ammar and colleagues (2010) found that 7 of 9 patients (5 males, 4 females ranging in age from 18 to 69 years) improved on 3,4-DAP alone (doses not specified). In another report (Anderson, 2008) where 3 patients received 3,4-DAP alone (doses not specified) and 3 patients received 3,4-DAP in combination with pyridostigmine or ephedrine, all 6 patients improved with treatment. Selcen and colleagues (2008) report 9 patients (3 males, 6 females ranging in age from 5 to 50 years) who received 3,4-DAP alone (n=4), or in combination with pyridostigmine (n=3) or ephedrine (n=2). One of the 2 children improved on 3, 4- DAP (10 mg TID), whereas the other child became worse after 3,4-DAP (5 mg TID) was added to her pyridostigmine regimen; 4 of 7 adults improved. Lashley and colleagues (2010) report follow-up of 10 patients with *DOK-7*-CMS mainly treated with ephedrine, with 2 patients (29 and 42 years of age) continued on 3,4-DAP treatment (15 or 30 mg QID). All patients improved over 6 to 8 months of follow-up.

With respect to *DPAGT1*-CMS, Finlayson and colleagues (2013) report 5 patients (2 males, 3 females ranging in age from 6 to 58 years), with 2 of 3 patients who received 3,4-DAP (doses not specified) having a favorable response to treatment. In another report, 2 children (both girls, 13 and 14 years of age) who received 3,4-DAP did not improve: one was on 3,4-DAP (30 mg/day) plus pyridostigmine and the other on 3,4-DAP (10 mg) (Selecen, 2014).

Two patients (7 and 48 years of age) with presynaptic CMS (with reduced quantal release) who had severe generalized weakness since early infancy initially responded to 3,4-DAP (dose not specified) and pyridostigmine, but then became refractory to treatment (Beeson, 2005). Both patients were wheelchair-bound and had multiple skeletal deformities. The younger patient could not speak or swallow and was respirator-dependent. In another report (Kinali, 2008), 4 of 5 children with CMS who received pyridostigmine and 3,4-DAP (doses not specified) showed a positive response.

8.4.3 Efficacy of Amifampridine in LEMS

A Phase 3, randomized, double-blind, placebo-controlled study (LMS-002) evaluated the efficacy and safety of amifampridine tablets 10 mg, as amifampridine phosphate (30-80 mg total daily dose) versus placebo in patients with LEMS. The 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 (February, 2015) for further details on these studies.

8.4.4 Safety of Amifampridine and Amifampridine Phosphate

Safety data collected from 1,454 patients or healthy volunteers in controlled study LMS-002 (LEMS) described above in Section 8.4.3, controlled and uncontrolled published studies of LEMS or other neurologic conditions, a 3-year safety surveillance study (ATU), and PK studies demonstrate amifampridine is well tolerated up to and including 80 mg/day (Firdapse Investigator Brochure, February 2015). The most common adverse events observed from the clinical safety data were perioral and peripheral paresthesias and gastrointestinal disorders (abdominal pain, nausea, diarrhea, epigastralgia). These events were typically mild or moderate in severity, and transient, seldom requiring dose reduction or withdrawal from treatment. In the pharmacogenomic study in healthy subjects (classified as either slow acetylators or fast acetylators), slow acetylators experienced >80% more drug-related AEs compared with fast acetylators (FIR-001).

Clinically significant or serious adverse events were infrequent in all studies for all indications. A total of 12 deaths were reported in the 1,454 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 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). No seizures have been reported in patients or healthy volunteers taking Firdapse since its commercial approval in December 2009 through 23 December 2014.

Amifampridine was implicated in at least 4 of these cases of seizure. 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 adult patient were palpitations (8/1,454; 0.56%), abnormal liver enzymes (6/1,454; 0.41%), QTc prolongation (2/1,454; 0.14%), and premature ventricular contraction/increased ventricular extrasystoles (2/1,454; 0.14%). Each of the following serious or clinically significant events was reported in a single patient: chorea, paresthesias, paroxysmal supraventricular tachycardia, cardiac arrest, drug-induced hepatitis, gastroesophageal reflux, increased lipase and amylase, aspiration pneumonia with confusion, and urinary tract infection with confusion.

Based upon the previous clinical studies involving the use of amifampridine in the treatment of Lambert-Eaton myasthenic syndrome (LEMS), there have been reports of provocation of bronchial asthma, respiratory failure, or respiratory disorder. These events are also part of

CMS symptoms; however, the risk may be more likely when the patient has asthma or respiratory disorder as a comorbidity with CMS.

8.5 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.

Risks of of study involvement have been minimized by:

1. Patients entering the study may already be on some formulation of 3,4-diaminopyridine and have demonstrated tolerability or;

2. Patients naïve to the medication are titrated to a tolerable and effective dose with open-label medication, under the observation of the Investigator. Thus, the development of adverse events or lack of efficacy is monitored by the Investigator during the step-wise titration and study medication dose can be reduced or discontinued at any point in the titration for either safety or lack of efficacy.

The pharmacokinetic half-life of amifampridine phosphate is short (1.8 hours), therefore discontinuation of medication will qickly terminate the effects, and mitigate adverse reactions.

This is a withdrawal study design looking at patient worsening on placebo; which is possible due to the short half-life of amifampridine phosphate. Therefore, patients must demonstrate a level of efficacy during the open-label titration period. This further reduces patient risk, by not continuing an experimental medication in patients who fail to demonstrate a benefit.

During the placebo withdrawal period, patients who deteriorate to a point that the Investigator assess to be lower than their baseline, open-label amifampridine phosphate is provided as to rescue the patient.

Refer to the Firdapse Investigator Brochure (February, 2015) for further information on benefit/risk of amifampridine.

8.6 Study Rationale

Clinical trials, case series, and case reports studying the efficacy of 3,4-DAP in patients with CMS have shown clinical benefit as described above in Section 8.4.2. Little controlled data are reported, and several of these studies had patients without genetic confirmation of CMS and lacked sensitive, objective, motor and electrophysiologic outcome measures to study efficacy. In light of above mentioned advancements in field of genetics, electrophysiological techniques, and motor function measures, a randomized placebo-controlled trial of 3,4-DAP in CMS patients is warranted. Thus, the purpose of this study (CMS-001) is to evaluate the efficacy and safety of amifampridine phosphate in patients diagnosed with subtypes of CMS.

9 STUDY OBJECTIVES

9.1 Primary Objectives

The primary objectives of the study are:

- To characterize the overall safety and tolerability of amifampridine phosphate compared with placebo in patients with CMS; and
- To assess the clinical efficacy of amifampridine phosphate compared with placebo in patients with CMS, based on improvement in subject global impression (SGI) and motor function measure (MFM 20 or 32) scores.

10 INVESTIGATIONAL PLAN

10.1 Overall Study Design and Plan

This is a randomized (1:1), double-blind, placebo-controlled, outpatient two-period two-treatment crossover study designed to evaluate the efficacy and safety of amifampridine phosphate in patients (2 years of age and above) diagnosed with CMS. The study is planned to be conducted at up to 5 sites in the United States and 2 sites in Canada, to include approximately 23 male and female patients. The planned duration of participation for each patient is approximately 56 days excluding the screening period, which can last up to 14 days.

All patients (parent or legal guardian) who sign an informed consent will be screened for eligibility to participate in the study, including: inclusion and exclusion criteria; medical and medication history; complete physical exam; standard 12-lead ECG; 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); and CMS genetic testing (if not previously done or available).

Those patients successfully completing initial screening will have procedures/assessments (see Table 3) conducted on Day 1 of the run-in period. Those not previously on 3,4-DAP or amifampridine phosphate will then embark on an open label up-titration of amifampridine phosphate dose based upon clinical benefit (assessed at clinic visit and telephone solicitation) for up to 4 weeks during run-in period, until stable dose and frequency of amifampridine phosphate is achieved for 7 days. If these patients have demonstrable increase of MFM 20 or MFM 32 scores of >20% during this period of open label uptitration of dose, patients will then be randomized to a Treatment Sequence on last day of open-label run-in period (Day 0).

Patients already receiving 3,4-DAP or amifampridine phosphate treatment for CMS, and meeting the applicable inclusion and exclusion criteria are eligible to participate in this study. The patient should report or investigator judges there is a history of meaningful improvement in motor function on 3,4-DAP or amifampridine phosphate treatment; improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants. Patients who are on a stable dose of amifampridine phosphate with a history of meaningful improvement in motor function, they can be randomized into Period 1. The patient should be on that stable dose and frequence of amifampridine phosphate for at least 1 week before being randomized to a Treatment Sequence. Those patients who are on a stable dose of 3,4-DAP will be transitioned to equivalent dose of amifampridine phosphate for 7 days prior to randomization to treatment.

Procedures/assessments, as detailed in Table 3, will be conducted before starting Period 1 study medication (i.e. Day 0). Administration of Period 1 study medication (amifampridine phosphate or placebo) begins after all assessments have been completed on Day 0. Every attempt should be made to have the same individual perform all assessments for a patient throughout the study, and after the same dose used for Day 0 assessments. Following Period 1, patients will be returned to the same stable dose administered at the end of the open-label run-in period for days 9-21, followed by Period 2 dosing for 8 days. Patients who were on a stable does of amifampriding phosphate with history of meaningful improvement prior to randomization in CMS-001, will be returned to the same stable dose from days 9-21, followed by Period 2 dosing for 8 days. After completion of of the study, patients will be eligible for expanded access program and receive open-label amifampridine phosphate at the same dose and frequency as established in the run-in phase of the study. Patients who were on stable dose of amifampriding phosphate with a history of meaningful improvement prior to randomization in CMS-001, will be returned to the same stable dose and frequency during

their participation in the expanded access program.

Following successful completion of the Run-in and randomization on Day 0, study visits will occur on Day 8 (+1 day), Day 21 (+1 day), and Day 29 (+1 day) or, if applicable, early discontinuation from the study. Note that should a shift in days occur (i.e. +1 day), then rest of schedule must shift to keep sequence and stabilization periods constant.

Safety and efficacy assessments will be made throughout the study as detailed in the Schedule of Assessments in Table 3 and Section 13.

Open-label Run-in

Amifampridine phosphate dosing will start on Day 1 of the Open-label Run-in and may be titrated upward every 3 to 4 days, per the dosing guidelines in Table 4, at the discretion of the investigator, for up to 4 weeks, with 1 week of stable dose and frequency before being randomized to a Treatment Sequence. Measurements of clinical improvement will be administered during the final period of dosing stability. Dosing can be increased or decreased by the investigator during the run-in phase prior to the last week of stable dosing. Randomization can only occur after the patient has been on a stable dose for at least 7 days.

For patients naïve to 3,4-DAP or amifampridine phosphate, a second screening event prior to randomization requires at least a 20% interval improvement in MFM 20 or 32 (scale use depends upon the age of patient), compared to Day 1 of the run-in period, to be eligible for randomization.

Patients already receiving amifampridine phosphate treatment for CMS meeting the inclusion and exclusion criteria are eligible to participate in this study. They must have a medical history showing improvement on amifampridine phosphate treatment; improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants. They can be randomized into Period 1 if on stable dose and frequency for 1 week before being randomized to a Treatment Sequence.

Those patients who are on a stable dose of 3,4-DAP with a history of meaningful improvement will be transitioned to equivalent dose of amifampridine phosphate for 7 days prior to randomization to treatment. Improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants.

Treatment Group A or B

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

Patients who successfully complete the open-label run-in and continue to meet all inclusion/exclusion criteria will be randomized (1:1 ratio) on the last day of the run-in period (Day 0) to either Sequence 1 or 2. Subjects randomized to Sequence 1 will receive Treatment A (amifampridine phosphate or placebo) in Period 1 and Treatment B (the other treatment) in Period 2. Subjects randomized to Sequence 2 will receive Treatment B (amifampridine or placebo) in Period 1 and Treatment A (the other treatment) in Period 2. Study medication (amifampridine phosphate tablets or placebo tablets) for Period 1 will be dispensed on Day 0, the last day of the Run-in, by the site pharmacist, according to the randomization schedule. The **administration of blinded medication will begin only after completion of all assessments of Day 0. The Day 0 assessments are performed while taking a dose of open-label amifampridine phosphate in the clinic, 40 minutes before starting the assessments**. Any supply of open-label amifampridine phosphate should be collected by the study site and stored before dispensing the Period 1 blinded medication.

The patient will receive either blinded amifampridine phosphate tablets or placebo tablets for 8 days as an outpatient, and a dose of the same medication on the day of scheduled study visit (Day 8) in the clinic, in order to facilitate efficacy assessments, under double-blind conditions. If the patient is on a BID or TID regimen during Period 1, the Day 8 assessments should occur after the same dose that corresponds to when assessments were done on Day 0. All unused medication and the container must be brought back to the study site at the end of Period 1. **The Day 8 medication is the same as double-blind medication taken for the previous Period 1 days.** Any unused portion of dispensed drug will be returned to the pharmacy before dispensing drug for the Re-Stabilization Period. A dose of medication for Day 8 must be administered by research study staff, in the clinic, in order to perform evaluations within specified time periods, as described in Section 10.3.3.

Re-stabilization Period (Days 9-21) (+1 day)

After Day 8 in-clinic evaluations, patients will return to open-label study drug, through Day 21 (same dose and frequency as at the end of run-in), as prescribed by investigator and dispensed by research pharmacist. No dose adjustments may occur. Patients who were on stable dose of amifampriding phosphate with history of meaningful improvement prior to randomization in CMS-001, will be returned to the same stable dose and frequency during the re-stabilization period.

Period 2 (Days 22-29) (+1 day)

Study medication will be dispensed by the site pharmacist on the last day of the Stabilization Period (i.e. Day 21), according to the randomization schedule. **Patients will start the blinded study medication only after completion of all of the Day 22 assessments, while taking open-label medication, 40 minutes before starting assessments.**

Per the crossover design, patients will receive the double-blind study medication (either amifampridine phosphate tablets or placebo tablets) during Period 2, for 8 days (Day 22 – 29) as an outpatient with a dose of the same medication on the day of scheduled study visit (Day 29), administered by study personnel in the clinic, to facilitate efficacy assessments, under double-blind conditions. If the patient is on a BID or TID regimen during Period 2, the Day 29 assessments should occur after the same dose that corresponds to when assessments were done on Day 0. Any unused portion of dispensed drug will be returned to the site before enrolling the patient in the expanded access ptogram and dispensing open-label drug.

Table 3. Schedule of Events

Study Assessment or Event [d]	Screening[qr]	Run-in (up to 4 weeks) [a]		Period I		Re-stabilization		Period II
		Start of Run-in	Last Visit	Days 1-8		Days 9-21		
	Days -14 to -1	Day 1	Day 0[b, c]	Days 1-7	Day 8 [c] (+1 d)	Days 9-20	Day 21 [c] (+1 d)	Days 22-29
Informed consent [e]	X							
Inclusion/exclusion criteria	X		X					
Randomization			X					
Medical history	X		X [f]					
CMS genetic testing [g]	X							
Complete physical exam [h]	X							
Abbreviated physical exam [i]			X		X		X	
Vital signs	X		X		X		X	
12-Lead ECG	X							
Clinical laboratory tests	X		X		X			
Pregnancy test [j]	X		X				X	
IP dispense		X	X [k]		X [l,]		X [k]	X
IP Administration [m,p]		X		X [n]	X [n]	X [n]	X[n]	X [n]

Table 3. Schedule of Events

Study Assessment or Event [d]	Screening[qr]	Run-in (up to 4 weeks) [a]		Period I		Re-stabilization		Period II
		Start of Run-in	Last Visit	Days 1-8		Days 9-21		
	Days -14 to -1	Day 1	Day 0[b, c]	Days 1-7	Day 8 [c] (+1 d)	Days 9-20	Day 21 [c] (+1 d)	Days 22-29
IP accountability			X		X		X	
SGI (patient/parent/ guardian/caregiver)			X		X		X	
MFM 20 or 32 (depending on age of patient)	X	X	X		X		X	
CGI-S	X		X		X		X	
CGI-I			X		X		X	
Stimulated single fiber EMG[o]	X				X			
Slurp Test[o]	X		X		X		X	
Adverse events[n]	X	X	X		X		X	
Concomitant medications	X	X	X		X		X	

CGI, Clinical Global Impression; CGI-I, Clinical Global Impression-Improvement; CMS, congenital myasthenic snydromes; CRF, case report form; EMG, electromyogram; IP, investigational product (amifampridine phosphate or placebo); MFM 20 or 32, motor function measure; SAE, serious adverse event; SGI, Subject Global Impression

[a] The first dose will be administered on Day 1. For the last 7 days of run-in, study drug dose must be stable before patient is eligible for randomization.

Table 3. Schedule of Events

Study Assessment or Event [d]	Screening[qr]	Run-in (up to 4 weeks) [a]		Period I		Re-stabilization		Period II
		Start of Run-in	Last Visit	Days 1-8		Days 9-21		
	Days -14 to -1	Day 1	Day 0[b, c]	Days 1-7	Day 8 [c] (+1 d)	Days 9-20	Day 21 [c] (+1 d)	Days 22-29

[b] All assessments and results must be available before randomization on Day 0.

[c] In-clinic visit.

[d] All safety assessments (vital signs, laboratory tests) are to be performed before the dose administered to the patient during the scheduled in-clinic visit unless specified otherwise. All efficacy assessments will be performed at standardized times relative to the dosing time of the day according to the efficacy assessments schedule in Section 10.7.

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

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

[g] CMS genetic testing will be conducted if not previously done or available. If previously done, a copy of the results should be included in the patient's CRF.

[h] Complete physical examination includes evaluation of all major body systems, including weight at all visits and height at Screening only (Section 10.6.6).

[i] An abbreviated physical exam may be performed as clinically indicated.

[j] Serum pregnancy tests will be obtained from female patients of childbearing potential only at Screening; urine dipstick for the remainder of the study.

[k] Patients will be provided blinded packages containing amifampridine phosphate or placebo depending on their group assignment.

[l] Open-label amifampridine phosphate will be dispensed at the Day 8 visit after all dosing and assessments have been completed for Period 1. Patient to get open-label amifampridine phosphate at the same dose and frequency as at the last run-in visit.

[m] Rescue dose amifampridine phosphate will be available in case of worsening symptoms in patients previously well-controlled on the drug during open-label run-in or during stabilization.

[n] SAE reporting commences when informed consent is signed. Non-serious adverse event reporting commences on Day 1 of run-in (Section 11).

[o] Stimulated single fiber EMG and Slurp test are optional assessments.

[p] It is recommended that doses of IP be taken with food.

[q] Screening and Day 1 visit may be cominbed into a single visit.

	Period II	
	Day 29 [c] (+1 d)	Early Discontinuation [c]
Study Assessment or Event [d]		X
Complete physical exam [h]	X	
Abbreviated physical exam		X
Vital signs	X	X
12-Lead electrocardiogram (ECG)	X	X
Clinical laboratory tests	X	X
Pregnancy test [j]	X	X
IP dispense		
IP administration	X	X
IP accountability	X	X
Subject Global Impression (SGI, patient/parent/guardian/caregiver)	X	X
Motor function measure (MFM) 20 or 32 (depending on age of patient)	X	X
Clinical Global Impression-Severity (CGI-S)	X	X
Clinical Global Impression-Improvement (CGI-I)	X	X
Stimulated single fiber electromyogram (EMG)[o]	X	X
Slurp test[o]	X	X
Adverse events[n]	X	X
Concomitant medications	X	X

10.2 Selection of Study Population

Criteria for participation in the study are provided in Sections 10.2.1 and 10.2.2.

10.2.1 Inclusion Criteria

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

1. Patient or parent 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, or the patient's legal guardian or caregiver with durable power of attorney can provide written informed consent. An assent form must also be signed if, in the judgement of the IRB/IEC/REB, children are capable of providing assent.
2. Male or female 2 years of age and above.
3. Body weight ≥10 kg.
4. Genetically-confirmed CMS involving acetylcholine receptor defect, Rapsyn deficiency, MuSK deficiency, Dok-7 deficiency, SYT2 mutations, SNAP25B deficiency, and fast channel syndrome.
5. In patients who are naïve to 3,4-DAP or amifampridine phosphate, MFM 20 or 32 score equal or less than 48 or 76, respectively, at Screening
6. In patients who are naïve to 3,4-DAP or amifampridine phosphate, improvement of >20% in MFM 20 or MFM 32 scores after open label period of uptitration of dose
7. In patients previously stabilized on 3,4-DAP or amifampridine phosphate, history of meaningful improvement in motor function (in the opinion of the investigator).
8. Willingness of patients receiving pyridostigmine, albuterol, ephedrine, or fluoxetine to remain on a stable dose of these medications throughout the study interval.
9. Female patients of childbearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG] at Screening); and must practice effective, reliable contraceptive regimen during the study. Acceptable methods of contraception include hormonal contraception (i.e., birth control pills, injected hormones, dermal patch or vaginal ring), intrauterine device, barrier methods (diaphragm, condom) with spermicide, or surgical sterilization (tubal ligation).

10. 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.

10.2.2 Exclusion Criteria

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

1. CMS subtype diagnosis of acetylcholinesterase deficiency, slow-channel syndrome, LRP4 deficiency, and plectin deficiency.
2. Cardiac conduction defects on Screening ECG.
3. Seizure disorder.
4. Clinically significant abnormal laboratory values at Screening, in the opinion of the investigator. Pregnancy or breastfeeding at Screening or planning to become pregnant at any time during the study.
5. Pregnancy or breastfeeding at Screening or planning to become pregnant at any time during the study.
6. Any systemic bacterial or other infection, which is clinically significant in the opinion of the investigator and has not been treated with appropriate antibiotics.
7. Treatment with an investigational drug (other than amifampridine or amifampridine phosphate), device, or biological agent within 30 days before Screening or while participating in this study.
8. Any other 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.
9. History of drug allergy to any pyridine-containing substances or any amifampridine phosphate excipient(s).

10.2.3 Removal of Patients from Treatment or Assessment

Patients/parent/guardian 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; or
- Patient becomes pregnant (refer to Section 11.4 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; or
- 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 (parent/guardian), 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.

10.2.4 Patient Identification and Randomization

Each patient will be assigned a unique patient identification number. Upon signing of the ICF, subjects will be assigned an ID composed of a two digit site number and a two digit subject number (e.g. site 1 subject 1 would be assigned 01-01). Screen failures that are allowed to be re-screend will keep the same site assigned ID. There are no plans to replace subjects that drop out of the study.

Randomization will be across sites to maintain the 1:1 ratio of drug:placebo assignment. The assignments to treatment (amifampridine phosphate or placebo) will be based on a computer-generated randomization code. A central point of contact will be provided to the site pharmacist to obtain the treatment sequence for the subject to be enrolled in Period 1 on the last day of the run-in period (Day 0).

10.2.5 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.

10.3 Treatments

10.3.1 Treatments Administered

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

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

Placebo: A placebo equivalent will be provided as tablets indistinguishable from the amifampridine phosphate tablets. The placebo will be administered consistent with the dose regimen of amifampridine phosphate.

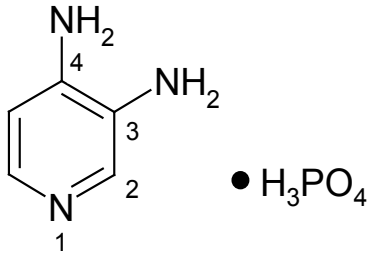
10.3.2 Identity of Investigational Product

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



10.3.2.1 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 department into suitably sized pharmacy bottles for patient use. Placebo will be provided as tablets indistinguishable from amifampridine phosphate. The amifampridine phosphate tablets and placebo tablets will be clearly labeled and the pharmacist is responsible for dispensing the amifampridine phosphate tablets or placebo tablets, as needed, for each patient.

Each bottle 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.

10.3.2.2 Storage

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

10.3.3 Directions for Administration

All doses of study treatment will be taken at home, except during the in-clinic study visit. If the patient takes the IP two or more times a day, then the patient should be given specific instructions on dosing relative to the time of their clinic visit to assure a dose will be given

during the in-clinic visits. A dose must be administered in the clinic in order to facilitate efficacy assessments. All safety assessments (vital signs, laboratory tests) are to be performed before the dose administered to the patient during the scheduled in-clinic visit. All efficacy assessments will be performed at standardized times relative to the dose administered in the clinic. In this case, the dose will be 40 minutes before the first efficacy assessment.

Assessment	**Start Time <u>After</u> Dose* (± 10 minutes unless otherwise specified)**
SGI	40 minutes
MFM 20 or 32	after SGI
Sitmulated Single fiber EMG^	after SGI
Slurp test^, CGI-S and CGI-I	At end of assessments

*Administration of medication represents Time 0 (minutes)
^Optional test

If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the MFM.

The dose of amifampridine phosphate will be individually determined by the investigator, within the bounds of a total daily dose of 10 mg to 80 mg, divided into doses taken 2 to 4 times per day generally taken with food (e.g. breakfast, lunch, dinner, and snack before bed) as prescribed by the investigator, based on optimal neuromuscular benefit (see Table 4).

All doses of study medication will be taken orally by mouth, with the following exceptions:

- children unable to swallow tablets will have the tablets crushed and mixed with a small amount of food; and
- children with a nasogastric or gastrostomy tube will have the tablets crushed and diluted in 5 to 10 mL of water and given through the tube.

Table 4. Dosing Guidelines

	Children[a]		
	Ages up to 3 Years	**Ages 3 to 16 Years**	**Ages >16 years**
Recommended starting dose	1 mg/kg/day, 3 times per day (to a maximum of 5 mg, 3 times a day)	5 mg, 3 times per day (15 mg/day total)	10 mg, 3 times per day (30 mg/ day total)
Initial dose escalation	May increase dose to 1 mg/kg, 4 times per day	May increase dose to 10 mg, 3 times per day (30 mg/day total)	May increase dose to 10 mg, 4 times per day (40 mg/day total)
Subsequent dose escalations	May increase dose by 1 mg/kg/day to the maximum daily dose of 60 mg/day	May increase dose to 10 mg, 4 times per day (40 mg/day total) May continue to titrate dose to 15 mg, 4 times per day (60 mg/day total)	May titrate dose up to 20 mg, 4 times per day (80 mg/day total)
Maximum dose:	60 mg/day	60 mg/day	80 mg/day

[a] Study medication will be crushed and mixed with a small amount of food for children unable to swallow tablets, and children with a nasogastric or gastrostomy tube will have the tablets crushed and diluted in 5 to 10 mL of water and given through the tube.

Titration during the run-in phase will be at investigator's discretion per guidelines in Table 4. The investigator may contact the patient every 3 to 4 days to evaluate clinical improvement and determine if an adjustment of study dose is needed. During double-blind, placebo-controlled treatment, rescue dose amifampridine phosphate will be available in case of worsening symptoms to a level that is worse than their baseline, prior to treatment. The Chief Medical Officer needs to be contacted to discuss breaking the blind.

10.3.4 Method of Assigning Patients to Treatment Groups

Patients will be randomized on the last day of the open-label run-in period (Day 0) to either Treatment Sequence 1 or 2, in a 1:1 ratio. Based upon the Treatment Sequence assigned, patients will receive either amifampridine phosphate or placebo in Period 1 and the other treatment in Period 2. A stabilization period using open-label amifampridine phosphate will occur between switches of amifampridine phosphate and placebo. IP will be administered under double-blind conditions for each Sequence.

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

10.3.5 Selection of Doses Used in the Study

The amifampridine phosphate dose is 10 mg to 80 mg total daily dose, given in 2 to 4 divided doses, with no single dose >15 mg in patients up to 16 years of age or >20 mg in patients >16 years of age. Safety of a single maximum dose of 20 mg is based on completed animal and *in vitro* pharmacology, PK, and toxicology studies.

10.3.6 Blinding

This is a double-blind study where both the patients (parent/guardian/caregiver) and investigator will be blinded to treatment assignment.

10.3.7 Treatment Compliance

Patients will be instructed to return all IP containers and remaining study 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.

10.3.8 Investigational Product Accountability

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

10.3.9 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.

10.4 Prior and Concomitant Medications

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

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

Medications prohibited during the study are listed in Table 5.

Table 5. Medications Prohibited During Study

Any investigational product (other than amifampridine phosphate) or an investigational medical device within 30 days before Screening

The following medicinal products should be use with caution in patients taking amifampridine phosphate:

Medicinal products known to cause cardiac QT prolongation

Medicinal products known to lower epileptic threshold

Medicinal products with atropinic effects

The concomitant use of amifampridine phosphate and medicinal products with atropinic effects may reduce the effect of both active substances and should be taken into consideration. Medicinal products with atropinic effects include tricyclic anti-depressants, most H1 atropinic anti-histamines, anticholinergic, anti-Parkinson medicinal products, atropinic antispasmodics, disopyramide, phenothiazine neuroleptics and clozapine.

Medicinal products with cholinergic effects

The concomitant use of amifampridine phosphate and medicinal products with cholinergic effects (e.g. direct or indirect cholinesterase inhibitors) may lead to an increased effect of both products and should be taken into consideration.

Non-depolarizing muscle relaxant acting medicinal products

The concomitant use of amifampridine phosphate and medicinal products with non-depolarizing muscle relaxant effects (e.g. mivacurium, pipercurium) may lead to a decreased effect of both products and should be taken into consideration.

Depolarizing muscle relaxant acting medicinal products

The concomitant use of amifampridine phosphate and medicinal products with depolarizing muscle relaxant effects (e.g. suxamethonium) may lead to a decreased effect of both products and should be taken into consideration.

10.5 Dietary or Other Protocol Restrictions

10.5.1 Dietary Restrictions

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

10.5.2 Contraception

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

10.6 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 3 and in Section 13.

10.6.1 Adverse Events

The determination, evaluation and reporting of AEs will be performed as outlined in Section 11.

10.6.2 Vital Signs

Specific visits for obtaining vital signs are provided in Table 3 and in Section 13. 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.

10.6.3 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 3 for the tests required by Protocol. The scheduled clinical laboratory tests are listed in Table 6.

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 6. Clinical Laboratory Tests

Liver Function Tests	Renal Function Tests	Electrolytes	Other
Alkaline phosphatase ALT (SGPT) AST (SGOT)	Blood urea nitrogen Creatinine	Sodium Potassium Chloride Calcium	Pregnancy test, if applicable CMS genetic testing [a]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CMS, congenital myasthenic syndromes; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.

[a] At Screening, if not previously done or available. If previously done, a copy of the CMS genetic testing results should be included in the patient's CRF.

10.6.4 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 3) and in Section 13. Female patients with a positive pregnancy test at Screening do not meet eligibility criteria for enrollment.

Refer to Section 11.4 for details on the reporting procedures to follow in the event of pregnancy.

10.6.5 Electrocardiogram

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 3) and in Section 13. Clinically significant changes from baseline will be recorded as AEs.

10.6.6 Physical Examination

A complete physical examination will be performed at the time points specified in the Schedule of Events in Table 3 and in Section 13. Complete physical examination will include assessments of general appearance as well as the following:

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

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

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

An abbreviated physical examination may be performed as clinically indicated. The procedures and assessments for performing an abbreviated physical examination will be at the discretion of the investigator.

10.7 Efficacy Variables

The timing of required evaluation is described in the Schedule of Events in Table 3 according to the sequence listed below.

Assessment	Start Time After Dose* (± 10 minutes unless otherwise specified)
SGI	40 minutes
MFM 20 or 32	after SGI
Stimulated Single fiber EMG	after MFM
Slurp test, CGI-S and CGI-I	At end of assessments

*Administration of medication represents Time 0 (minutes)

If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the MFM.

10.7.1 Subject Global Impression

The SGI (Farrar, 2001) is a 7-point scale on which the patient rates their global impression of the effects of a study treatment (1 = terrible to 7 = delighted). The SGI will be assessed by the patient or the patient's parent/guardian/caregiver if the patient is unable to complete the SGI. The SGI has demonstrated concordance with the physician's assessment of improvement (Dodick, 2007). Instructions for the SGI are provided in Appendix 1 and the CMS-001 Study Reference Manual.

10.7.2 Motor Function Measure

The standard MFM 32 (Bérard, 2005) evaluates the severity and progression of motor function and is applicable to all degrees of disease severity, in both ambulant and nonambulant patients. It is not, however, well suited as an outcome measure in young children because of the time required to complete the MFM and difficulty in completion in terms of childrens' cognitive and motor development. A short-form (MFM 20) (de Lattre, 2013) will be used in this study for patients 2 years up to 7 years of age, with each of 20 items scored on a 4-point Likert scale (based on patient's best abilities without assistance): standing and transfers (8 items); axial and proximal motor function (8 items); and distal motor function (4 items). Total MFM 20 score ranges from 0 to 60. The MSM 32 will be used for patients 7 years of age and older, with each of 32 items scored on a 4-point Likert

scale (based on patient's best abilities without assistance): standing and transfers (13 items), axial and proximal motor function (12 items), and distal motor function (7 items). Total MFM 32 score ranges from 0 to 96. Higher MFM 20 or 32 scores indicate more functional improvement.

MFM 20 or 32 will be administered at the protocol specified time points by the same well trained evaluator throughout the study. Instructions for conducting the MFM 20 and MFM 32 are provided in Appendix 2 and Appendix 3, respectively, and in the CMS-001 Study Reference Manual.

10.7.3 Clinical Global Impression Scales

The CGI score is a 2-part observer-rated instrument that assesses 1) severity of the patient's disease (CGI-S) at a given point in time and 2) change from baseline (CGI-I). This instrument is widely used and well validated (Busner, 2009). The investigator will complete the 7-point CGI-S based on his/her experience of severity in the CMS population as a whole as the point of reference. Instructions for the CGI-S are contained in Appendix 4 and the CMS-001 Study Reference Manual.

The CGI-I captures the investigator's global impression of the patient's improvement or worsening from baseline status. The 7-point scale is scored by the investigator based on changes in symptoms, behavior, and functional abilities. Instructions for the CGI-I are contained in Appendix 5 and the CMS-001 Study Reference Manual.

10.7.4 Stimulated Single Fiber Electromyogram

Stimulated single fiber EMG is a method to assess the integrity of the neuromuscular junction. The principal of stimulated single fiber EMG is to measure the time variability of the muscle fiber action potentials as they are generated by the discharges of the motor neuron (SFEMG using voluntary activation) versus the variability of a single muscle fiber potential (SFEMG using motor axonal stimulation). In infants, young children, or patients having difficulty in making a controlled activation, stimulated jitter analysis is preferable. From a technical standpoint, facial muscles such as the frontalis and orbicularis oculi are the easiest to record by stimulating the distal branch of the facial nerve supplying them with a monopolar needle electrode. The latter has less associated stimulation artifact and better control of the stimulating impulse. Since the recordings are made with a disposable concentric needle electrode, the term "jitter analysis" is preferred as being semantically more correct than single fiber EMG. Stimulated jitter analysis will be performed by a certified electromyographer. Local anesthetic agent will be applied to the site of needle electrode

examination 30 minutes before the procedure. Not all patients can tolerate the procedure so this test is optional.

10.7.5 Slurp Test

Patient's with neuromuscular disorders experience increasing weakness of bulbar-innervated muscles that may result in aspiration or catastrophic airway compromise. The "Slurp" test is a non-invasive way of assessing bulbar function (Hudspeth 2006), particularly in children. Four ounces (120 mL) of water is placed in a cup. The patient is instructed to drink the entire contents of the cup through a standard flex straw as quickly as possible, making a loud slurping sound at the end. The duration of time from the start of drinking the water to the slurp sound will be measured. This test is optional. Slurp tests will be initiated during the up-titration phase by parents or investigators until reliable performance is achieved, thereafter only at identified places in the protocol timeline.

11 REPORTING ADVERSE EVENTS

11.1 Adverse Events

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

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

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

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

The study period during which all non-serious AEs will be reported begins after informed consent is obtained and the first administration of study drug through the last visit (Study Day 29) 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 11.2.

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 11.2 for SAE definition). Severity (as in mild, moderate or severe headache) is not equivalent to seriousness, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

The investigator will determine the severity of each AE using the following Common Terminology Criteria for Adverse Events (CTCAE) v 4 grades defined in Table 7 (the event will be recorded on the source documents and AE CRF) (Appendix 5). Events that are CTCAE grades 4 and 5 are serious events and require completion of both an SAE form and AE CRF. Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4 as stated below.

Table 7. Categories of Severity for CTCAE Criteria

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

Activities of Daily Living (ADL)

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

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

The investigator will suggest the relationship of an AE to the IP and will record it on the source documents and AE CRF, using the relationship categories defined in Table 8.

Table 8. Description of Relationship to Adverse Event Categories

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

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

11.2 Serious Adverse Events

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

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

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

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

The reporting period for SAEs begins after informed consent is obtained and continues through 4 weeks after the last dose or at the early discontinuation 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. 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 to Catalyst.

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

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

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

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

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

11.3 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.

11.4 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.

11.5 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/EC/REB is notified at the same time." The reporting period for urgent safety measures is the period from the time of signing of the ICF through the completion of the last study visit. Investigators are required to report any urgent safety measures within 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.

11.6 Medical Monitor Contact Information

Contact information and additional requirements will be provided in the CMS-001 Study Reference Manual.

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

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

Email: gingenito@catalystpharma.com

12 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 CMS.

13 STUDY PROCEDURES

13.1 Screening Visit

An ICF must be signed and dated by the patient, parent or legal guardian, the investigator or designee, and witness (if required) before any study-related procedures are performed. Refer to Section 10.4 for prohibited medications.

After ICF signed, the patient will be screened for enrollment into the study. The study activities listed below will be performed during the 1 to 14 days that constitute the Screening visit.

- Informed Consent;
- Assessment of Inclusion/Exclusion criteria;
- Demographics (sex, race, ethnic origin, age);
- Medical history, including allergy history and number of hospitalizations or ER visits in last 6 months;
- CMS genetic testing, if not previously done and report available;
- 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;
- For females of child bearing potential, a serum pregnancy test will be taken at Screening.;
- MFM 20 or 32;
- Stimulated single fiber EMG (optional);
- CGI-S;
- Slurp test (optional);
- Assessment of SAEs; and
- Assessment of concomitant medications.

13.2 Open-label Run-in

Patients, previously not on amifampridine phosphate treatment for CMS may visit the study site for weekly visits for up to 4 weeks throughout the run-in period for the assessments and

procedures listed in Table 3. Efficacy measurements will be performed during or at the end of run-in to document improvement or maintenance of optimal benefit of study drug. Additional visits or telephonic interactions are allowed as necessary.

At the end of this period (Day 0), patients must have been on a stable dose and frequency for 7 days and show at least a 20% improvement in MFM 20 or 32 (depending on the age of patient) from Day 1 of Run-in.

Patients aleady receiving amifampridine phosphate treatment for CMS meeting the inclusion and exclusion criteria are eligible to participate in this study. They can be randomized into Period 1 if on stable dose and frequency for 1 week before being randomized to a Treatment Sequence. Improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants.

Patients who are deemed eligible will be administered amifampridine phosphate for Day 0 at the study site, by the study personnel, and have the assessments/procedures listed below completed, in relation to the time of receiving study medication on Day 0, before randomization.

- Confirmation of Inclusion/Exclusion criteria;
- Assessment of AEs/SAEs;
- Abbreviated physical exam with weight;
- Vital signs (seated position), including SBP, DBP, heart rate, respiration, and body temperature;
- Clinical laboratory tests;
- Urine pregnancy test in females of childbearing potential only;
- Concomitant medications;
- IP accountability;
- Efficacy assessments, including:
  - MFM 20 or 32;
  - SGI (patient/parent/guardian/caregiver);
  - CGI-S;
  - CGI-I; and
  - Slurp test (optional).

Assessment	Start Time After Dose* (± 10 minutes unless otherwise specified)
SGI	40 minutes
MFM 20 or 32	after SGI
Slurp test, CGI-S and CGI-I	At end of assessments

*Administration of medication represents Time 0 (minutes)

The site pharmacy will dispense bottles containing blinded amifampridine phosphate or placebo tablets, depending on the patient's Treatment Sequence assignment, for daily outpatient administration for 7 days (Days 1-7). Administration of blinded study medication will begin with the next scheduled dose following the Day 0 baseline assessment on open-label medication. (see Section 13.3).

13.3 Period 1

Administration will be continued on an outpatient basis for a total of 7 days (Days 1-7).

On Day 8 (+1) patients will be given a dose of the same study medication as the previous 7 days by the study personnel, at the site, so that the assessments/procedures listed below will be completed in relation to the time of study medication dosing.

- Assessment of AEs/SAEs;
- Abbreviated physical exam with weight;
- Vital signs (seated position), including SBP, DBP, heart rate, respiration, and body temperature;
- Clinical laboratory tests;
- Concomitant medications;
- IP accountability;
- Efficacy assessments, including:
  - MFM 20 or 32;
  - SGI (patient/parent/guardian/caregiver);
  - Stimulated Single fiber EMG (optional);
  - CGI-S;
  - CGI-I; and

- Slurp test (optional).

Assessment	Start Time After Dose* (± 10 minutes unless otherwise specified)
SGI	40 minutes
MFM 20 or 32	after SGI
Stimulated Single fiber EMG	after MFM
Slurp test, CGI-S and CGI-I	At end of assessments

*Administration of medication represents Time 0 (minutes)

If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the MFM.

Open-label amifampridine phosphate will be dispensed at the Day 8 visit for administration during the stabilization period, starting with the next scheduled dose after Day 8 assessments (see Section 13.4).

13.4 Re-stabilization Period

Patients will return to their prior open-label amifampridine phosphate dose established in the run-in phase for 2 weeks, Day 9 through Day 21.

Patients will report to the study site on Day 21 (+1 day) and have the assessments/procedures listed below completed.

- Assessment of AEs/SAEs;
- Abbreviated 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;
- Concomitant medications;
- IP accountability;
- Efficacy assessments, including:
  - MFM 20 or 32;

- SGI (patient/parent/guardian/caregiver);
- CGI-S;
- CGI-I; and
- Slurp test (optional).

Assessment	**Start Time <u>After</u> Dose* (± 10 minutes unless otherwise specified)**
SGI	40 minutes
MFM 20 or 32	after SGI
Slurp test, CGI-S and CGI-I	At end of assessments

*Administration of medication represents Time 0 (minutes)

A The slurp test (optional), CGI-S and CGI-I assessments should be done following completion of the MFM.

The site will dispense bottles containing amifampridine phosphate or placebo tablets, depending on the patient's Treatment Sequence assignment, for Period 2 (Days 22-28). Administration of blinded study medication will begin with the next scheduled dose after Day 21 assessments are completed (see Section 13.5).

13.5 Period 2

Patients will the blinded study medication they **<u>did not</u>** receive in Period 1. Administration will be continued on an outpatient basis for a total of 7 days (Days 22-28).

Patients will report to the study site on Day 29 (+1 day) and receive a dose of the same study medication they received for the previous 7 days, under the supervision of the study personnel, in order to time the following assessments/procedures in relation to the medication dose.

- 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;

- Urine pregnancy test in females of childbearing potential only;
- Concomitant medications;
- IP accountability;
- Efficacy assessments, including:
  - MFM 20 or 32;
  - SGI (patient/parent/guardian/caregiver);
  - Stimulated single fiber EMG (optional);
  - CGI-S;
  - CGI-I; and
  - Slurp test (optional).

Assessment	**Start Time <u>After</u> Dose* (± 10 minutes unless otherwise specified)**
SGI	40 minutes
MFM 20 or 32	after SGI
Stimulated Single fiber EMG	after MFM
Slurp test, CGI-S and CGI-I	At end of assessments

*Administration of medication represents Time 0 (minutes)

If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the MFM.

After completion of the above procedures/assessments, patients will be eligible for an expanded access program.

13.6 Early Discontinuation Visit

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

- Assessment of AEs/SAEs;
- Complete physical examination with weight;

- Vital signs (seated position), including SBP, DBP, heart rate, respiration, and body temperature;
- Standard resting 12-lead ECG;
- Clinical laboratory tests;
- Urine pregnancy test in females of childbearing potential only;
- Concomitant medications;
- IP accountability; and
- Efficacy assessments, including:
  - MFM 20 or 32;
  - SGI (patient/parent/guardian/caregiver);
  - Stimulated Single fiber EMG (optional);
  - CGI-S;
  - CGI-I; and
  - Slurp test (optional).

The date of the last dose of study medication should be recorded in relation to Early Discontinuation assessments.

14 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, including 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), SAE reporting and drug accountability records.

Data quality control and analysis will be performed by Catalyst or a designee, based on a predefined analysis plan.

15 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

15.1 Determination of Sample Size

Assuming a standardized between-treatment difference of 0.5, 23 patients per sequence will ensure power of 90% for the 2-sided test at the 0.05 level using the standard 2-by-2 crossover analysis.

15.2 Safety Analysis

Safety analyses will be conducted on the safety population (i.e. all patients who receive at least 1 dose of amifampridine phosphate or placebo). The safety analysis will be descriptive and will be presented on observed data only. All safety data, and corresponding Change From Baseline (CFB) if appropriate, will be listed.

15.3 Adverse Events

All treatment-emergent adverse events (TEAEs) will be summarized by the treatment at the time of onset. Counts and percentages will be presented by treatment for each observed system organ class (SOC) and preferred term (PT) as defined in MedDRA. Summaries by level of severity and relationship to treatment will be presented by treatment at the time of occurrence. Listings of all deaths, SAEs, and discontinuations due to AE will be provided.

15.4 Laboratory Tests

For each laboratory parameter, descriptive statistics will be presented for the observed value and CFB by treatment at the time of the assessment. The frequency and percentage of patients who experience abnormal (i.e. outside of reference ranges) laboratory values will be presented by treatment at the time of the assessment. Clinically significant abnormalities will be collected as AEs.

15.5 Other Safety Assessments

Summary statistics for vital signs, physical examinations, and ECG parameters will be presented by treatment at the time of the assessment.

15.6 Efficacy Analysis

The following provides a summary of the planned statistical analyses. Details will be provided in a separate Statistical Analysis Plan (SAP), which will be finalized prior to unblinding. Any inconsistency between the SAP and the protocol will be noted in the SAP.

Efficacy analyses will be performed for 2 datasets:

Full Analysis Set (FAS): This population consists of all randomized patients who receive at least 1 dose of IP (amifampridine phosphate 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.

If the PP Population is the same as the FAS, then the results will be presented only for the FAS. Exclusion from the FAS and PP Population will be finalized prior to database lock and subsequent unblinding.

In addition to the following, summary statistics will be provided by treatment and period for CGI-I, CGI-S, Change From Baseline (CFB) for CGI-S, the optional Slurp Test, and variables associated with the optional SFEMG.

15.7 Primary Efficacy Analysis

The analysis of CFB for SGI is the primary efficacy analysis and will be performed using the standard analysis for a 2-by-2 crossover design. Summary statistics for SGI and CFB for SGI will be presented by treatment and period. P-values <0.05 wil be considered statistically significant.

15.8 Secondary Efficacy Analysis

The total score for MFM and the subtotal for each of the three dimensions (Standing and transfer, Axial and proximal motor function, and Distal motor function) will be standardized by the possible maximum for both MFM 20 and MFM 32. The CFB for these standardized scores will be analyzed using the standard analysis for a 2-by-2 crossover design for MFM 20 and MFM 32 separately and pooled, with the latter being the secondary and the separate analyses being supportive. The total scores, subtotals for each dimension, and the corresponding standardized scores will be summarized by treatment and period for MFM 20 and MFM 32 separately and standardized scores will be summarized by treatment and period for MFM 20 and MFM 32 pooled. P-values <0.05 wil be considered statistically significant.

15.9 Changes in the Conduct of the Study

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.

16 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.

17 CASE REPORT FORMS AND SOURCE DOCUMENTS

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

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

18 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.

19 RETENTION OF RECORDS

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

All study records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until (1) there are no pending or contemplated marketing applications in an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator/institution should retain patient identifiers for at least 15 years after the completion or discontinuation of the study. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory

requirements or by a Catalyst agreement. Catalyst must be notified and will assist with retention should investigator/institution be unable to continue maintenance of patient files for the full 15 years. It is the responsibility of Catalyst to inform the investigator /institution as to when these documents no longer need to be retained.

20 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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22 INVESTIGATOR RESPONSIBILITIES

22.1 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 in the course of 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.

23 SIGNATURE PAGE

Protocol Title: A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized, Outpatient Two-period Two-treatment Crossover Study to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with Congenital Myasthenic Syndromes (CMS)

Protocol Number: CMS-001

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.

24 APPENDICES

Appendix 1 Subject Global Impression (SGI)

The SGI will be assessed at the protocol-specified time points (see Table 3) by the patient or the patient's parent/guardian/caregiver if the patient is unable to complete the SGI.

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

1=Terrible

2= Mostly dissatisfied

3= Mixed

4=Partially satisfied

5= Mostly satisfied

6= Pleased

7= Delighted

Refer to the CMS-001 Study Reference Manual for additional information.

Appendix 2 Motor Function Measure (MFM 32 or 20)

The MFM 32 will be used to evaluate the severity and progression of motor function in patients 7 years of age and older. For patients 2 years up to 6 years of age, the MFM 20 will be used to evaluate the severity and progression of motor function. The MFM 32 or 20 (depending on age) will be administered at the protocol specified time points (see Table 3) by the same well trained evaluator throughout the study.

Each of the 32 items listed below will be graded using a 4-point Likert scale based on the patient's best abilities without any assistance:

0 Cannot initiate the task

1 Partially performs the task

2 Performs the movement incompletely, or completely but imperfectly (compensatory movements, position maintained for an insufficient duration of time, slowness, uncontrolled movement)

3 Performs the task fully and "normally"; the movement is controlled, mastered, directed, and performed at constant speed

The 20 motor function measures comprising the MFM20 are marked with ☺ (child <7 years old)

Total score ranges from 0 to 96 when summing the 32 items and from 0 to 60 when summing the 20 items.

Items MFM 32 (from 7 to 60 years	**☺ Items MFM 20 (child <7 years old)**
1. ☺ SUPINE, HEAD IN MIDLINE POSITION**:** holds the head for 5 seconds in midline position and turns it completely from one side to the other. ***comments* :**	
2. SUPINE: raises the head and maintains the raised position for 5 second *comments* :	
3. ☺ SUPINE: flexes the hip and knee more than 90° by raising the foot during the whole movement *comments* : side : right : ❑ left : ❑	
4. ☺ SUPINE, LEG SUPPORTED BY EXAMINER: from the plantar flexion, dorsiflexes the foot to at least 90° in relation to the lower part of the leg. *comments*: side : right : ❑ left : ❑	
5. ☺ SUPINE: raises the hand and moves it to the opposite shoulder. *comments*: side : right : ❑ left : ❑	
6. ☺ SUPINE, LOWER LIMBS HALF-FLEXED, KNEECAPS AT THE ZENITH AND FEET RESTING ON THE MAT SLIGHTLY APART: maintains for 5 seconds the starting position then raises the pelvis ; the lumbar spine, the pelvis and the thighs are aligned and the feet slightly apart. *comments*:	
7. ☺ SUPINE: turns over into prone and frees both upper limbs from under the trunk. *comments*: side : right : ❑ left : ❑	
8. SUPINE: without upper limb support sits up. *comments*:	
9. ☺ SEATED ON THE MAT: without upper limb support, maintains the seated position for 5 seconds and is then capable of maintaining contact 5 seconds between the two hands. *comments*:	

Items MFM 32 (from 7 to 60 years	**☺ Items MFM 20 (child <7 years old)**
10. ☺ Seated on the mat, THE tennis ball placed in front of the PERSON without upper limb support, leans forward, touches the ball and sits back again. comments:	
11. ☺ SEATED ON THE MAT: without upper limb support, stands up. *comments*:	
12. ☺ STANDING: without upper limb support, sits down on the chair with the feet slightly apart. *comments*:	
13. SEATED ON THE CHAIR: without upper limb support nor leaning against the back of the chair, maintains the seated position for 5 seconds, with the head and trunk in midline position. *comments*:	
14. ☺SEATED ON THE CHAIR OR IN THE WHEELCHAIR, HEAD IN FLEXION: from head in complete flexion, raises the head then maintains it raised for 5 seconds, the head stays in midline position throughout the movement and the holding position. *comments*:	
15. SEATED ON THE CHAIR OR IN THE WHEELCHAIR, FOREARMS ON THE TABLE BUT NOT ELBOWS: places both hands on top of the head at the same time while the head and trunk remain in midline position. *comments*:	
16. SEATED ON THE CHAIR OR IN THE WHEELCHAIR, THE PENCIL ON THE TABLE: without moving the trunk, reaches the pencil with one hand, forearm and hand off the table with the elbow in full extension at the end of the movement. *comments:* side : right : ❑ left : ❑	
17. SEATED ON THE CHAIR OR IN THE WHEELCHAIR, 10 COINS ON THE TABLE: successively picks up and holds 10 coins in one hand during a 20-second period.	

Items MFM 32 (from 7 to 60 years	**☺ Items MFM 20 (child <7 years old)**

comments:

side : right : ❑ left : ❑

18. ☺ SEATED ON THE CHAIR OR IN THE WHEELCHAIR, ONE FINGER PLACED IN THE CENTER OF THE FIXED CD: goes round the edge of the CD with the same finger without hand support on the table.

comments:

side : right : ❑ left : ❑

19. SEATED ON THE CHAIR OR IN THE WHEELCHAIR, THE PENCIL ON THE TABLE: picks up the pencil and draws a continuous series of loops inside the frame and over its full length touching the top and bottom line of the frame.

Trial n° 1

Trial n° 2

comments:

side : right : ❑ left : ❑

20. SEATED ON THE CHAIR OR IN THE WHEELCHAIR, HOLDING THE SHEET OF PAPER: tears the sheet of paper folded in 4, beginning from the fold edge.

comments:

21. ☺ SEATED ON THE CHAIR OR IN THE WHEELCHAIR, THE TENNIS BALL ON THE TABLE: *picks up the ball, and turns the hand over completely holding the ball.*

comments:

side : right : ❑ left : ❑

22. ☺ SEATED ON THE CHAIR OR IN THE WHEELCHAIR, ONE FINGER PLACED IN THE CENTER OF THE DIAGRAM: raises the finger and places it successively on the 8 drawings without touching the lines.

comments:

side : right : ❑ left : ❑

23. ☺ SEATED ON THE CHAIR OR IN THE WHEELCHAIR, UPPER LIMBS ALONG THE TRUNK: places the two forearms and/or the hands on the table at the same time without moving the trunk. *comments*
24. ☺ SEATED ON THE CHAIR: without upper limb support, stands up with the feet slightly apart. *comments*
25.☺ STANDING WITH UPPER LIMB SUPPORT ON EQUIPMENT: without upper limb support, maintains a standing position for 5 seconds with the feet slightly apart, the head, trunk and limbs in midline position *comments:*
26. STANDING WITH UPPER LIMB SUPPORT ON EQUIPMENT: without upper limb support, raises the foot for 10 seconds. *comments:* side support: right : ❑ left : ❑
27. ☺ STANDING: without support, touches the floor with one hand and stands up again. *comments:*
28. STANDING WITHOUT SUPPORT: takes 10 steps forward on both heels. *comments:*
29. STANDING WITHOUT SUPPORT: takes 10 steps forward on a line. *comments:*
30.☺ STANDING WITHOUT SUPPORT: runs 10 meters. *comments:*
31. STANDING ON ONE FOOT WITHOUT SUPPORT: hops 10 times in place. *comments:* side support : right : ❑ left : ❑
32. ☺ STANDING WITHOUT SUPPORT: without upper limb support, manages to squat and gets up twice in a row. *comments*:

Appendix 3 Clinical Global Impression-Severity (CGI-S)

The CGI-S will be used to assess the severity of the patient's disease. The investigator will complete the 7-point CGI-S, based on his/her experience of severity in the CMS population as a whole as the point of reference, at the protocol-specified time points (see Table 3).

Considering your total clinical experience with this particular population, how ill is the patient at this time?

1 = Normal, not at all ill

2 = Borderline ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill patients

Refer to the CMS-001 Study Reference Manual for additional information.

Appendix 4 Clinical Global Impression-Improvement (CGI-I)

The CGI-I will be used to capture the investigator's global impression of the patient's improvement or worsening from baseline status. The investigator will complete the 7-point CGI-I, based on changes in symptoms, behavior, and functional abilities, at the protocol-specified time points (see Table 3).

Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment.

Compared to the patient's condition at baseline, how much has it changed?

1 = Very much improved

2 = Much improved

3 = Minimally improved

4 = No change

5 = Minimally worse

6 = Much worse

7 = Very much worse

Refer to the CMS-001 Study Reference Manual for additional information.

Appendix 5 Common Terminology Criteria for Adverse Events (CTCAE) Version 4

Refer to:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix 6: Protocol Amendment 1

PURPOSE: The purpose of this amendment is as follows:

Administrative change to clarify the original intent of a reasonable duration of time (at least 3 months) between the last SGI and MFM 20 or MFM 30 assessments and the first incidence of these assessments in this protocol.

Risk: these administrative changes provide clarity on duration between testing to avoid testing bias, adding no additional risk to the patient.

MODIFICATIONS TO PROTOCOL:

- **<u>Bold and underlined text</u>:** Changed Text
- ~~**Bold and strike through text**~~**:** Deleted Text
- ***Bold and italicized text:*** Added Text

On Page 1, under Date of Protocol, added text to indicate this is protocol amendent 1.

Amendment 1: 2 February 2016

On Page 5, first paragraph folowing header, added text:

They must have not been previously assessed for improvement in subject global impression (SGI) and motor function measure (MFM 20 or 32) scores ***within 3 months prior to participating in this study*** to avoid testing bias.

On Page 34, third paragraph under the header **<u>Open-label Run-in</u>**, deleted text:

Patients already receiving amifampridine phosphate treatment for CMS meeting the inclusion and exclusion criteria are eligible to participate in this study. They can be randomized into Period 1 if on stable dose and frequency for 1 week before being randomized to a Treatment Sequence. They must have a medical history showing improvement on amifampridine phosphate treatment: improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants ~~**and will not be administered to minimize potential for testing bias.**~~

On Page 62, third paragraph under section 13.2, text was added:

Patients aleady receiving amifampridine phosphate treatment for CMS meeting the inclusion and exclusion criteria are eligible to participate in this study. They can be randomized into Period I if on stable dose and frequency for 1 week before being randomized to a Treatment Group. They must have a medical history showing improvement on amifampridine phosphate treatment: improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants. They must have not been previously assessed for improvement in subject global impression (SGI) and motor function measure (MFM 20 or 32) scores ***within 3 months prior to participating in this study*** to avoid testing bias.

Appendix 7: Protocol Amendment 2

PURPOSE: The purpose of this amendment is as follows:

Administrative changes to correct the use of the the term1) "sequence" from "period" and 2) outpatient versus office visit.

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

MODIFICATIONS TO PROTOCOL:

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

On Page 1, under Date of Protocol, added text to indicate this is protocol amendent 2.

Amendment 2: 7 March 2016

On page 6:

Period~~Sequence~~ II (Day 29) (+1 day)

On page 44, first paragraph:

A central point of contact will be provided to the site pharmacist to obtain the treatment sequence for the subject to be enrolled in **Period I**~~Sequence~~ on the last day of the run-in period (Day 0).

On Page 63, paragraph under table:

The site will dispense bottles containing amifampridine phosphate or placebo tablets, depending on the patient's Treatment Group assignment, for daily outpatient administration for 7 days (Days 1-7). Administration of blinded study medication will begin with the first morning dose on Day 1 of **Period I**~~Sequence~~ (see Section 13.3).

On Page 63, under section 13.3, Period I:

On Day 1, patients will begin administration of randomized study medication (amifampridine phosphate or placebo tablets) with the first morning dose. Administration will be continued on an outpatient basis for a total of 7~~8~~ days (Days 1-7~~8~~).

Appendix 8: Protocol Amendment 3

PURPOSE: The purpose of this amendment is as follows:

To increase the age range eligible for the study, expand the statistical analysis section of the protocol, increase the number of patients in the study, and update previous instructional language regarding dosing on the days of clinic evaluations.

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

MODIFICATIONS TO PROTOCOL:

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

On Page 1, under Date of Protocol, added text to indicate this is protocol amendent 3.

Amendment 3: 7 July 2016

On Page 2, under Contact Information, changed text with updated Catalyst phone number.

Tel: +1 305 420-3200, ext. 123

On Page 3, under Study Site, changed text to 5 sites.

Multicenter at up to 5 sites in the United States

On Page 3, under Objectives, changed word children for patients.

- **To characterize the overall safety and tolerability of amifampridine phosphate compared with placebo in patients with CMS; and**
- **To assess the clinical efficacy of amifampridine phosphate compared with placebo in patients with CMS, based on improvement in subject global impression (SGI) and motor function measure (MFM 20 or 32) scores.**

On Page 3, under Study Design and Plan, deleted 10 male and female patients and added 23.

The study is planned to include up to 23 male and female patients. The planned duration of participation for each patient is approximately 56 days, excluding the screening period, which can last up to 14 days.

On Page 4, under Name of Invesigational Product, deleted 7 days and added 8 days.

Study medication at the stable dose or placebo, will be dispensed by the site pharmacist, according to the randomization schedule, beginning the morning of Day 1 for the 8 day Period 1. Following experimental Period 1, patients will be returned to the stable dose administered at the end of the open-label run-in period from days 9-21, followed by Period 2 dosing for 8 days (Days 22-29).

On Page 4, under Name of Invesigatinal Product, changed text from 7 days to 8 days.

Study medication at the stable dose or placebo, will be dispensed by the site pharmacist, according to the randomization schedule, beginning the morning of Day 1 for the 8 day Period 1. Following experimental Period 1, patients will be returned to the stable dose administered at the end of the open-label run-in period from days 9-21, followed by Period 2 dosing for 8 days (Days 22-29).

On Page 4, under Name of Invesigatinal Product, changed ±1 and added ±2.

Patients taking open-label amifampridine phosphate following completion of Study Day 29 visit will return to the study site for a final safety assessment on Day 36 (±2 days).

On Page 5, under Name of Invesigatinal Product, added "at least".

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

On Page 5, under Period 1 (Day 1-8) (+1day), added text.

7 days as an outpatient, and a dose of the same medication on the day of scheduled study visit on Day 8 in the clinic in order to facilitate efficacy assessments, under double-blind conditions. If the patient is on a BID or TID regimen during Period 1, then any planned dosing following the dose given by study personnel in the clinic should be completed on Day 8 with tablets dispensed for Period 1 after all scheduled visit assessments are completed. Any unused portion of dispensed drug will be returned to the pharmacy before dispensing drug for the Re-Stabilization Period.

On Page 6, under Period 2 (Days 22-29) (±2days), added text.

blinded study appropriate medication/placebo for Period 2 for 7 days (Day 22 – 28) as an outpatient and a dose of the same medication on the day of scheduled study visit on Day 29 in the clinic in order to facilitate efficacy assessments, under double-blind conditions. If the patient is on a BID or TID regimen during Period 2, then any planned dosing following the dose given by study personnel in the clinic should be completed on Day 29 with tablets dispensed for Period 2 after all scheduled visit assessments are completed. Any unused portion of dispensed drug will be returned to the pharmacy before dispensing open-label drug to begin dosing on Day 30 through the Final Safety Asssessment on Day 36.

Follow-up and Final Safety Assessment (Days 30-36) (±2 days)
Patients will be administered amifampridine phosphate at the same dose and frequency established as the stable dose in the open-label run in phase until Day 36± 2 days, under open-label conditions.

On Page 6, after Final Safety Assessment (Day 36) (±2 days) changed ±1 and added ±2.

Final Safety Assessment (Day 36) (±2 days)

Patients taking open-label amifampridine phosphate following Study Day 29 visit will return to the study site for a final safety assessment on Day 36 (±2 days).

On Page 6, under Name of Investigational Products, change from 2 to 7 years of age.

2. Male or female age 2 years and above.

On Page 7, under Name of Investigational Products, deleted "two forms of".

9. Female patients of childbearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG] at Screening); and must practice ~~**two forms of**~~ effective, reliable contraceptive regimen during the study. Acceptable methods of contraception include hormonal contraception (i.e., birth control pills, injected hormones, dermal patch or vaginal ring), intrauterine device, barrier methods (diaphragm, condom) with spermicide, or surgical sterilization (tubal ligation).

On Page 7, under Criteria for Inclusion and Exclusion, deleted text.

~~**4. Abnormal liver function tests at Screening.**~~

~~**5. Abnormal kidney function tests at Screening.**~~

~~**6. Abnormal electrolyte values at Screening.**~~

On Page 7, under Criteria for Inclusion and Exclusion, added text.

4. Clinically significant abnormal laboratory values at Screening, in the opinion of the investigator.

On Page 9, under Criteria for Evaluation, change from word child to individual.

• MFM 20 or 32 (MFM 20 (individual <7 years) and MFM 32 (individual ≥ 7 years));

On Page 9, under Criteria for Evaluation, deleted words "head area" and added face.

An approximate 20-minute video will be obtained at each protocol specified time point and the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech; as age permits.

On Page 9, under Statistical Methods, deleted text.

The sample size for this study is based on clinical considerations related to the epidemiology

of the disease **~~and not on a formal statistical calculation.~~**

On Page 9, under Statistical Methods, changed sample size.

Assuming a standardized between-treatment difference of 0.5, 23 patients per sequence will ensure power of 90% for the 2-sided test at the 0.05 level using the standard 2-by-2 crossover analysis.

On Page 10, under Efficacy Analysis, deleted text.

~~The variability of outcome variables in this rare disease is unknown and the available sample size is such that there is almost certainly insufficient power to observe differences that will be found to be statistically significant. Thus, no formal statistical testing will be done.~~

On Page 10, under Efficacy Analysis, changed text.

If the PP Population is the same as the FAS, then the results will be presented only for the FAS. Exclusion from the FAS and PP Population will be finalized prior to database lock and subsequent unblinding.

Summary statistics will be provided by treatment and period for CGI-I, CGI-S, Change From Baseline (CFB) for CGI-S, the optional Slurp Test, and variables associated with the optional SFEMG.

The analysis of CFB for SGI is the primary efficacy analysis and will be performed using the standard analysis for a 2-by-2 crossover design. Summary statistics for SGI and CFB for SGI will be presented by treatment and period. P-values <0.05 wil be considered statistically significant.

The total score for MFM and the subtotal for each of the three dimensions (Standing and transfer, Axial and proximal motor function, and Distal motor function) will be standardized by the possible maximum for both MFM 20 and MFM 32. The CFB for these standardized scores will be analyzed using the standard analysis for a 2-by-2 crossover design for MFM 20 and MFM 32 separately and pooled, with the latter being the secondary and the separate analyses being supportive. The total scores, subtotals for each dimension, and the corresponding standardized scores will be summarized by treatment and period for MFM 20 and MFM 32 separately and standardized scores will be summarized by treatment and period for MFM 20 and MFM 32 pooled. P-values <0.05 wil be considered statistically significant.

On Page 20, under Investigator and Study Administrative Structure, changed text with updated Catalyst phone number.

Tel: +1 305 420-3200, ext. 123

On page 32, under Study Rationale, deleted and added text.

Clinical trials, case series, and case reports studying the efficacy of 3,4-DAP in patients with CMS have shown clinical benefit as described above in Section 8.4.2. Little controlled data are reported **~~in infants and young patients,~~** and several of these studies had patients without genetic confirmation of CMS and lacked sensitive, objective, **~~rapid~~** motor and

electrophysiologic outcome measures to study efficacy ~~**especially in infants and young children**~~. In light of above mentioned advancements in field of genetics, electrophysiological techniques, and motor function measures, a randomized placebo-controlled trial of 3,4-DAP in CMS patients is warranted. Thus, the purpose of this study (CMS-001) is to evaluate the efficacy and safety of amifampridine phosphate in ***patients*** diagnosed with subtypes of CMS.

On page 32, under Primary Objectives, change word children to patients.

• To characterize the overall safety and tolerability of amifampridine phosphate compared with placebo in **patients** with CMS; and

• To assess the clinical efficacy of amifampridine phosphate compared with placebo in **patients** with CMS, based on improvement in subject global impression (SGI) and motor function measure (MFM 20 or 32) scores.

On page 32, under Overall Study Design and Plan, deleted and added text.

This is a randomized (1:1), double-blind, placebo-controlled, outpatient two-period two-treatment crossover study designed to evaluate the efficacy and safety of amifampridine phosphate in ~~**children**~~ ***patients*** (2~~-17~~ **years of age and above**) diagnosed with CMS. The study is planned to be conducted at up to ~~**3**~~**5** sites in the United States and will include~~ **up to approximately 10** **23** male and female patients. The planned duration of participation for each patient is approximately 56 days excluding the screening period, which can last up to 14 days.

On page 34, under Overall Study Design and Plan, added text.

After completion of of the study, patients will be eligible for expanded access program and receive open-label amifampridine phosphate at the same dose and frequency as established in the run in phase of the study.

On Page 35, under Treatment Group A or B, added text.

Beginning on Day 1 of Period 1, the patient will receive either amifampridine phosphate tablets or placebo tablets for 7 days as an outpatient, and a dose of the same medication on the day of scheduled study visit on Day 8 in the clinic in order to facilitate efficacy assessments, under double-blind conditions. If the patient is on a BID or TID regimen during Period 1, then any planned dosing following the dose given by study personnel in the clinic should be completed on Day 8 with tablets dispensed for Period 1, after all scheduled visit assessments are completed. All unused medication and the container must be brought back to the study site at the end of Period 1. The Day 8 medication is the same as double-blind medication taken for the previous Period 1 days

On Page 37, under Table 3, text changed from Every Week to Start of Run-in.

Start of Run-in

On Page 37, Table 3 under Day 1, text deleted

~~**(+1d)**~~

On Page 37, Table 3 X on IP accountability and Day 1, deleted.

~~**X**~~

On Page 38, Table 3 under Day 1, text deleted

~~**(+1d)**~~

On page 38, Table 3, under Screening, Stimulated Single Fiber EMG, added text.

X

On Page 39, Table 3, after d, added text.

dose administered to the patient during the scheduled in-clinic visit

On Page 39, Table 3, after l, added text.

after all dosing and assessments have been completed for Period 1.

On Page 39, Table 3, after m, added text.

Open-label amifampridine phosphate will be dispensed at the Day 29 visit after all dosing and assessments have been completed for Period 2. Patient to get open-label amifampridine phosphate at the same dose and frequency as at the last run-in visit.

On Page 39, Table 3, after q, added text.

It is recommended that doses of IP be taken with food.

On Page 38, Table 3, after r, added text.

Screening and Day 1 visit may be cominbed into a single visit.

On Page 40, Table 3, under Complete physical exam, added text.

Abbreviated physical exam

On Page 41, under Inclusion Criteria, changed text.

2. **Male or female 2 years of age and above.**

On Page 41, under Inclusion Criteria, added text.

4. ***Genetically-confirmed CMS involving acetylcholine receptor defect, Rapsyn deficiency, MuSK deficiency, Dok-7 deficiency, SYT2 mutations, SNAP25B deficiency, and fast channel syndrome.***

On Page 42, under Exclusion Criteria, added text.

4. ***Clinically significant abnormal laboratory values at Screening, in the opinion of the investigator***

On Page 45, under Exclusion Criteria, deleted text.

~~**4. Abnormal liver function tests at Screening.**~~

~~**5. Abnormal kidney function tests at Screening.**~~

~~**6. Abnormal electrolyte values at Screening.**~~

On Page 44, under Directions for Administration, added text.

All doses of study treatment will be taken at home, except during the in-clinic study visit. If the patient takes the IP two or more times a day, then the patient should be given specific instructions on dosing relative to the time of their clinic visit to assure a dose will be given during the in-clinic visit. A dose must be administered in the clinic in order to facilitate efficacy assessments. All safety assessments (vital signs, laboratory tests) are to be performed before the dose administered to the patient during the scheduled in-clinic visit. All efficacy assessments will be performed at standardized times relative to the dose administered in the clinic. In this case, the dose will be 40 minutes before the first efficacy assessment.

On Page 46, in the table, changed text.

~~**45 minutes**~~ **after SGI**

~~**140 minutes**~~ **after MFM**

~~**160 minutes**~~ **after video**

On Page 46, under table, added text.

At the end of the MFM testing, the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits.

If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the video of the patient's face.

On Page 46, under table third paragraph, deleted text.

~~**as dispensed with food**~~

On Page 47, under Method of Assigning Patients to Treatment Groups, deleted text.

~~**Subjects randomized to Sequence I will receive Treatment A (amifampridine phosphate) in Period 1 and Treatment B (placebo) in Period 2. Subjects randomized to Sequence II will receive Treatement B (placebo) in Period 1 and Treatment A (amifampridine phosphate) in period 2.**~~

On Page 47, under Method of Assigning Patients to Treatment Groups, added text.

Based upon the Treatment Sequence assigned, patients will receive either amifampridine phosphate or placebo in Period 1 and the other treatment in Period 2.

On Page 52, in the table, changed text.

~~**45 minutes**~~ **after SGI**

~~**140 minutes**~~ **after MFM**

~~**160 minutes**~~ **after video**

On Page 52, under Table, added text.

At the end of the MFM testing, the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits.

If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the video of the patient's face.

On Page 52, under Table, deleted text.

~~**The MFM testing will be videod. At the end of the MFM testing, the patient's head area will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech.**~~

~~**If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the video of the patient's head area.**~~

On Page 59, under Pregnacy, changed text.

~~**Drug Exposure via Parent Form**~~ **Pregnancy Reporting Form**

On Page 60, under Medical Monitor Contact Information, changed text.

Tel: +1 305 420-3200, ext. 123

On Page 61, under Screening Visit, deleted text.

After ~~patient's parent or legal guardian has signed an~~ ICF *signed*, the *patient* will be screened for enrollment into the study. The study activities listed below will be performed during the 1 to 14 days that constitute the Screening visit.

On Page 61, under Screening Visit, added text.

- ***CMS genetic testing, if not previously done and report available***
- ***Stimulated single fiber EMG***

On Page 61, under Screening Visit, deleted text.

- ~~**SGI (patient/parent/guardian/caregiver);**~~

On Page 62, under Open-label Run-in, deleted text.

~~**They must have a medical history showing improvement on amifampridine phosphate treatment:**~~

On Page 63, deleted text from table.

~~**45 minutes**~~ **after SGI**

~~**140 minutes**~~ **after MFM**

~~**Stimulated Single fiber EMG 160 minutes**~~

On Page 63, under Table, added text.

At the end of the MFM testing, the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits.

On Page 63, under Table, deleted text.

~~**The MFM testing will be videod. At the end of the MFM testing, the patient's head area will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech.**~~

~~**If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the video of the patient's head area.**~~

On Page 63, under Period 1, deleted text and added text

On Day 8 (+1) patients will be given a dose of ~~their~~ *the same study medication as the previous 7 days* ~~study medication~~ by the study personnel, at the site, so that the

assessments/procedures listed below will be completed in relation to the *time of study medication* dosing ~~of the study medication~~.

On Page 64, in the table, changed text.

~~**45 minutes**~~ **after SGI**

~~**140 minutes**~~ **after MFM**

~~**160 minutes**~~ **after video**

On Page 64, under table added text.

At the end of the MFM testing, the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits

On Page 64, under table deleted text.

~~**The MFM testing will be videod. At the end of the MFM testing, the patient's head area will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech.**~~

On Page 65, under Re-stabilization Period, deleted and added text.

- ~~**Clinical laboratory tests;**~~
- **Urine pregnancy test** ~~**(dipstick)**~~ ***in females of childbearing potential only;***

On Page 65, deleted text from table.

~~**45 minutes**~~ **after SGI**

~~**140 minutes**~~ **after MFM**

~~**Stimulated Single fiber EMG 160 minutes**~~

On Page 65, under Table deleted and added text

At the end of the MFM testing, the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits ~~**The MFM testing will be videod. At the end of the MFM testing, the patient's head area will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech.**~~

~~**If the stimulated single fiber EMG (optional assessment) is not to be performed, then t**~~**The slurp test (optional), CGI-S and CGI-I assessments should be done following completion of the video of the patient's face.**

On Page 66, under Period 2, added text.

Patients will report to the study site on Day 29 (+1 day) ***and receive a dose of the same study medication they received for the previous 7 days, under the supervision of***

the study personnel, in order to time the following ~~**and the**~~ **assessments/procedures** ~~**listed below will be completed**~~ ***in relation to the medication dose.***

On Page 67, under Period 2, changed text.

- ~~**Complete**~~ **Abbreviated physical exam with weight;**

On Page 67, under Period 2, changed text

- ***Stimulated*** ~~**S**~~**single fiber EMG**;

On Page 67, on Table, deleted and added text.

~~**45 minutes**~~ **after SGI**

~~**140 minutes**~~ **after MFM**

~~**160 minutes**~~ **after video**

On Page 67, under Safety Follow-Up, changed text.

Patients taking open-label amifampridine phosphate, following Study Day 29 visit, will return to the study site on Day 36 (±2~~+1~~ days) for a final safety assessment, including:

On Page 67, under Safety Follow-Up, deleted text.

- ~~**Clinical laboratory tests;**~~

On Page 67, under Safety Follow-Up, added text.

- ***IP accountability.***

On Page 70, under Determination of Sample Size, changed text.

15.1 Determination of Sample Size

Assuming a standardized between-treatment difference of 0.5, 23 patients per sequence will ensure power of 90% for the 2-sided test at the 0.05 level using the standard 2-by-2 crossover analysis.

15.2 Safety Analysis

Safety analyses will be conducted on the safety population (i.e. all patients who receive at least 1 dose of amifampridine phosphate or placebo). The safety analysis will be descriptive and will be presented on observed data only. All safety data, and corresponding Change From Baseline (CFB) if appropriate, will be listed.

15.3 Adverse Events

All treatment-emergent adverse events (TEAEs) will be summarized by the treatment at the time of onset. Counts and percentages will be presented by treatment for each

observed system organ class (SOC) and preferred term (PT) as defined in MedDRA. Summaries by level of severity and relationship to treatment will be presented by treatment at the time of occurrence. Listings of all deaths, SAEs, and discontinuations due to AE will be provided.

15.4 Laboratory Tests

For each laboratory parameter, descriptive statistics will be presented for the observed value and CFB by treatment at the time of the assessment. The frequency and percentage of patients who experience abnormal (i.e. outside of reference ranges) laboratory values will be presented by treatment at the time of the assessment. Clinically significant abnormalities will be collected as AEs.

15.5 Other Safety Assessments

Summary statistics for vital signs, physical examinations, and ECG parameters will be presented by treatment at the time of the assessment.

15.6 Efficacy Analysis

The following provides a summary of the planned statistical analyses. Details will be provided in a separate Statistical Analysis Plan (SAP), which will be finalized prior to unblinding. Any inconsistency between the SAP and the protocol will be noted in the SAP.

Efficacy analyses will be performed for 2 datasets:

Full Analysis Set (FAS): This population consists of all randomized patients who receive at least 1 dose of IP (amifampridine phosphate 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.

If the PP Population is the same as the FAS, then the results will be presented only for the FAS. Exclusion from the FAS and PP Population will be finalized prior to database lock and subsequent unblinding.

In addition to the following, summary statistics will be provided by treatment and period for CGI-I, CGI-S, Change From Baseline (CFB) for CGI-S, the optional Slurp Test, and variables associated with the optional SFEMG.

15.7 Primary Efficacy Analysis

The analysis of CFB for SGI is the primary efficacy analysis and will be performed using the standard analysis for a 2-by-2 crossover design. Summary statistics for SGI and CFB for SGI will be presented by treatment and period. P-values <0.05 wil be considered statistically significant.

15.8 Secondary Efficacy Analysis

The total score for MFM and the subtotal for each of the three dimensions (Standing and transfer, Axial and proximal motor function, and Distal motor function) will be standardized by the possible maximum for both MFM 20 and MFM 32. The CFB for these standardized scores will be analyzed using the standard analysis for a 2-by-2 crossover design for MFM 20 and MFM 32 separately and pooled, with the latter being the secondary and the separate analyses being supportive. The total scores, subtotals for each dimension, and the corresponding standardized scores will be summarized by treatment and period for MFM 20 and MFM 32 separately and standardized scores will be summarized by treatment and period for MFM 20 and MFM 32 pooled. P-values <0.05 wil be considered statistically significant.

Appendix 9: Protocol Amendment 4

PURPOSE: The purpose of this amendment is as follows:

To formally remove the videotaping of patients from the protocol, clarify the start and stop times of Periods 1 and 2, blinded medication dosing, and remove the Day 36 visit. The patient is either on a stable dose of amifampridine phosphate or has been titrated over a period of 4 weeks. Also, the patient is observed on open label medication for 2 weeks during the restabilization period. Therefore, the Day 36 visit on open label medication adds no new information to the efficacy or safety profile of amifampridine phosphate and the patient may go directly into the expanded access program.

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

MODIFICATIONS TO PROTOCOL:

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

On Page 1, under Clinical Study Protocol, added text

Date of Amendment 4: ***25 April 2017***

On Page 3, under Study Site, added text

Multicenter at up to 5 sites in the United States ***and 3 sites in Canada***

On Page 4, under Name of Investigational Product, added text

Patients on a stable dose of amifampridine phosphate with a history of meaningful improvement in motor function are eligible immediately for randomization.

On Page 4, under Name of Investigational Product, added and deleted text

Study medication at the stable dose or placebo, will be dispensed by the site pharmacist, according to the randomization schedule, beginning ~~**the morning of Day**~~ ***with the dose following completion of assessments on Day 0 and*** ~~**1**~~ for the 8 day Period 1.

On Page 4, under Name of Investigational Product, added text

Patients who were on a stable does of amifampriding phosphate with history of meaningful improvement prior to randomization in CMS-001, will be returned to the same stable dose from days 9-21, followed by Period 2 dosing for 8 days (Days 22-29).

On Page 4, under Name of Investigational Product, added text

Patients who were on stable dose of amifampriding phosphate with history of meaningful improvement prior to randomization in CMS-001, will be returned to the same stable dose and frequency during their participation in the expanded access program.

On Page 4, under Name of Investigational Product, deleted text

~~**Patients taking open-label amifampridine phosphate following completion of Study Day 29 visit will return to the study site for a final safety assessment on Day 36 (±2 days).**~~

On Page 5, under Name of Investigational Product, added and deleted text

Measurements of clinical improvement will be administered at the outset and ~~**during this time, timed**~~ ***repeated*** as clinically indicated ***during the titration period***, to ~~**demonstrate**~~ ***assess*** open-label efficacy

On Page 5, under Name of Investigational Product, deleted text

~~**They must have not been previously assessed for improvement in subject global impression (SGI) and motor function measure (MFM 20 or 32) scores within 3 months prior to participating in this study to avoid testing bias.**~~

On Page 5, under Name of Investigational Product, deleted and added text

Patients already receiving 3,4-DAP or amifampridine phosphate treatment for CMS, and meeting the inclusion and exclusion criteria are eligible to participate in this study~~**. if they have a medical**~~***The patient should report or investigator judges there is a*** history of improvement on 3,4-DAP or amifampridine phosphate treatment; improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants.

On Page 5, under Name of Investigational Product, added and deleted text

~~**Beginning on Day 1 of Period 1**~~***Only after assessments are completed on Day*** **0**, the patient will ***begin to*** receive either amifampridine phosphate tablets or placebo tablets for ~~**7**~~ **8** days as an outpatient, ~~**and**~~ ***with*** a dose of the same medication on the day of scheduled study visit (Day 8) in the clinic, in order to facilitate efficacy assessments, under double-blind conditions. If the patient is on a BID or TID regimen during Period 1, ~~**then any planned dosing following the dose given by study personnel in the clinic should be completed on Day 8 with tablets dispensed for Period 1 after all scheduled visit assessments are completed**~~***.the Day 8 assessments should occur after the same dose that corresponds to when assessments were done on Day 0.*** Any unused portion of ***double-blind*** dispensed drug will be returned to the ~~**pharmacy**~~ ***site*** before dispensing drug for the Re-Stabilization Period.

On Page 5, under Re-Stabilization Period (Days 9-21) (+1 day), added text ***Patients who were on stable dose of amifampriding phosphate with history of meaningful improvement prior to randomization in CMS-001, will be returned to the same stable dose and frequency during the re-stabilization period.***

On Page 6, under Period 2 (Days 22-29) (+1 day)

After completion of Period 1 and the re-stabilization period, according to randomization sequence, patients will receive the blinded study medication/placebo for Period 2 for ~~7~~ **8** days (Day 22 – ~~28~~***29***) as an outpatient ~~**and**~~ ***with*** a dose of the same medication on the day of scheduled study visit (Day 29) in the clinic, in order to facilitate efficacy assessments, under double-blind conditions. If the patient is on a BID or TID ~~**regemen**~~ ***regimen*** during Period 2, ~~**then any planned dosing following the dose given by study personnel in the clinic should be completed on Day 29 with tablets dispensed for Period 2 after all scheduled visit assessments are completed**~~***the Day 29 assessments should occur after the same dose that corresponds to when assessments were done on Day 0***. Any unused portion of ***double-blind*** dispensed drug will be returned to the ~~**pharmacy**~~ ***site*** before ***enrolling the patient in the expanded access program and*** dispensing open-label drug. ~~**to begin dosing on Day 30 through the Final Safety Asssessment on Day 36.**~~

~~**Follow-up and Final Safety Assessment (Days 30-36) (±2 days)**~~

~~**Patients will be administered amifampridine phosphate at the same dose and frequency established as the stable dose in the open-label run-in phase until Day 36± 2 days, under open-label conditions.**~~

~~**Final Safety Assessment (Day 36) (±2 days)**~~

~~**Patients taking open-label amifampridine phosphate following Study Day 29 visit will return to the study site for a final safety assessment on Day 36 (±2 days).**~~

On Page 6, under Name of Investigational Product, added text

1. Patient or parent 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, or the patient's legal guardian or caregiver with durable power of attorney can provide written informed consent. An assent form must also be signed if in the judgement of the ***IRB/IEC/REB*** the children are capable of providing assent.

On Page 7, under Criteria for Inclusion and Exclusion, added text

5. ***In patients who are naïve to 3,4-DAP or amifampridine phosphate,*** MFM 20 or 32 score equal or less than 48 or 76, respectively, at Screening.

6. In patients ***who are*** naïve to ***3,4-DAP or*** amifampridine phosphate, improvement of >20% in MFM 20 or MFM 32 scores after open label period of uptitration of dose

7. In patients ***who are*** previously stabilized on 3,4-DAP ***or amifampridine phosphate, a*** history of meaningful improvement in motor function (in ***the*** opinion of ***the*** investigator).

On Page 7, under Name of Investigational Product, added text

8. Willingness of patients receiving pyridostigmine, ~~**prednisone,**~~ albuterol, ephedrine, or fluoxetine to remain on a stable dose of these medications throughout the study interval.

On Page 8, under Duration of Treatment, deleted and added text

~~**Up to**~~ ***Approximately*** ~~**63**~~***56*** days (excluding up to 14-day screening period) after enrollment.

On Page 9, under Efficacy, deleted text

- ~~**Patient video of the face;**~~

~~**Videography, using standardized technology and equipment, will be used to evaluate patient progress. An approximate 20-minute video will be obtained at each protocol specified time point and the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech; as age permits.**~~

On Page 8, under Criteria for Inclusion and Exclusion, deleted and added text

7. Treatment with an investigational drug (other than ~~**amifampridine**~~ ***3,4-DAP*** or amifampridine phosphate), device, or biological agent within 30 days before Screening or while participating in this study.

8. Any other 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 confounds the assessment of the patient.

9. History of drug allergy to any pyridine-containing substances or any amifampridine phosphate excipient(s).

~~**9.10. History of drug allergy to any pyridine-containing substances or any amifampridine or amifampridine phosphate excipient(s).**~~

On Page 18, under 6.1 Independent Ethics Committee, deleted and added text

(~~IRB~~*IRB/IEC/REB*)

On Page 19, under 6.3 Patient Information and Informed Consent, deleted and added text

(~~IRB~~*IRB/IEC/REB*)

On Page 32, under 10.1 Overall Study Design and Plan, deleted and added text

The study is planned to be conducted at up to 5 sites in the United States ***and 2 sites in Canada~~, and will~~to*** include approximately 23 male and female patients

On Page 33, under 10.1 Overall Study Design and Plan, deleted and added text

The planned duration of participation for each patient is ***approximately 56 up~~ to 63~~*** days excluding the screening period, which can last up to 14 days.

All patients ~~**who have had a**~~**(**parent or legal guardian**)** ***who*** sign an informed consent will be screened for eligibility to participate in the study, including: inclusion and exclusion criteria; medical and medication history; complete physical exam; standard 12-lead ECG; 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); and CMS genetic testing (if not previously done or available).

On Page 33, under 10.1 Overall Study Design and Plan, deleted and added text

Patients already receiving 3,4-DAP or amifampridine phosphate treatment for CMS, and meeting the applicable inclusion and exclusion criteria are eligible to participate in this study. The patient should report or investigator judges there is a history of meaningful improvement in motor function on 3,4-DAP or amifampridine phosphate treatment; improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants. Patients who are on a stable dose of amifampridine phosphate with a history of meaningful improvement in motor function, they can be randomized into Period 1. The patient should be on that stable dose and frequence of amifampridine phosphate for at least 1 week before being randomized to a Treatment Sequence. ~~**Patients on a stable dose of amifampridine phosphate with history of meaningful improvement in motor function are eligible immediately to randomization, while**~~ ***T~~t~~hose patients who are*** on a stable dose of 3,4-DAP will be transitioned to equivalent dose of amifampridine phosphate for 7 days prior to randomization to treatment.

On Page 33 and 34, under 10.1 Overall Study Design and Plan, deleted and added text

Administration of Period 1 study medication (amifampridine phosphate or placebo) begins ~~**with the morning dose the day after randomization (i.e. Day 1)**~~***after all assessments have been completed on Day 0.*** Every attempt should be made to have the same individual perform all assessments for a patient throughout the study, and ~~**at approximately the same time of day**~~***after the same dose used for Day 0 assessments.*** Following Period 1, patients will be returned to the same stable dose administered at the end of the open-label run-in period for days 9-21, followed by Period 2 dosing for 8 days. ~~**Patients will be taking open-label amifampridine phosphate following Study Day 29 visit and will return to the study site for a final safety assessment on Day 36 (±2 days day).**~~ ***Patients who were on a stable does of amifampriding phosphate with history of meaningful improvement prior to randomization in CMS-001, will be returned to the same stable dose from days 9-21, followed by Period 2 dosing for 8 days.*** After completion of of the study, patients will be eligible for expanded access program and receive open-label amifampridine phosphate at the same dose and frequency as established in the run-in phase of the study. ***Patients who were on stable dose of amifampriding phosphate with history of meaningful improvement prior to randomization in CMS-001, will be returned to the same stable dose and frequency during their participation in the expanded access program.***

Following successful completion of the Run-in and randomization on Day 0, study visits will occur on Day 8 (+1 day), Day 21 (+1 day), and Day 29 (+1 day), ~~**and Day 36 (±2 days) (final safety assessment)**~~ or, if applicable, early discontinuation from the study. Note that should a shift in days occur (i.e. +1 day), then rest of schedule must shift to keep sequence and stabilization periods constant.

On Page 34, under Open-Label Run-in, moved text

Patients already receiving amifampridine phosphate treatment for CMS meeting the inclusion and exclusion criteria are eligible to participate in this study. **They must have a medical history showing improvement on amifampridine phosphate treatment; improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants.** They can be randomized into Period 1 if on stable dose and frequency for 1 week before being randomized to a Treatment Sequence. ~~**They must have a medical history showing improvement on amifampridine phosphate treatment: improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants.**~~

On Page 34, under Open-Label Run-in, added text

Those patients who are on a stable dose of 3,4-DAP with a history of meaningful improvement will be transitioned to equivalent dose of amifampridine phosphate for 7 days prior to randomization to treatment. Improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants.

On Page 35, under Period 1 (Days 1-8) (+1 day), deleted and added text

The **administration** **of** **blinded** **medication will begin only after completi*on of*~~ng~~ all assessments of Day 0. The Day 0 assessments are performed while taking a dose of open-label amifampridine phosphate in the clinic, 40 minutes before starting the assessments**.

On Page 35, under Period 1 (Days 1-8) (+1 day), deleted and added text.

Study medication (amifampridine phosphate tablets or placebo tablets) for Period 1 will be dispensed on Day 0, the last day of the Run-in, by the site pharmacist, according to the randomization schedule., ~~**with**~~ ***The administration of blinded medication will*** ~~**to**~~ begin ~~**with the morning dose the day after randomization (i.e. Day 1)**~~***only after completing all assessments of the Day 0. The Day 0 assessments are performed while taking a dose of open-label amifampridine*** ~~***phophate***~~***phosphate in the clinic, 40 minutes before starting the assessments.*** ~~**Beginning on Day 1 of Period 1, t**~~ ***Any supply of open-label amifampridine phosphate should be collected by the study site and stored before dispensing the Period 1 blinded medication.***

The patient will receive either ***blinded*** amifampridine phosphate tablets or placebo tablets for 7 8 days as an outpatient, and a dose of the same medication on the day of scheduled study visit (Day 8) in the clinic, in order to facilitate efficacy assessments, under double-blind conditions. If the patient is on a BID or TID regimen during Period 1, ~~**then any planned dosing following the dose given by study personnel in the clinic should be completed on Day 8 with tablets dispensed for Period 1, after all scheduled visit assessments are completed.**~~***the Day 8 assessments should occur after the same dose that corresponds to when assessments were done on Day 0.***

On Page 35, under Re-stabilization Period (Days 9-21) (+1 day), deleted text

After Day 8 in-clinic evaluations, patients will return to open-label study drug ~~**the next day, from Day 9**~~ through Day 21 (same dose and frequency as at the end of run-in), as prescribed by investigator and dispensed by research pharmacist.

On Page 35, under Re-stabilization Period (Days 9-21) (+1 day), added text

No dose adjustments may occur. ***Patients who were on stable dose of amifampriding phosphate with history of meaningful improvement prior to randomization in CMS-001, will be returned to the same stable dose and frequency during the re-stabilization period.***

On Page 36, under Period 2 (Days 22-29) (+1 day), deleted and added text

Study medication will be dispensed by the site pharmacist on the last day of the Stabilization Period (i.e. Day 21), according to the randomization schedule. Patients will start the blinded study medication ~~**with the morning dose on Day**~~ ***22after completing all of the Day 22 assessments, while*** ~~***on***~~ ***taking open-label medication, 40 minutes before starting assessments***

Per the crossover design, patients will receive the double-blind study medication (either amifampridine phosphate tablets or placebo tablets) during Period 2, for ~~**7**~~ ***8*** days (Day 22 – 2~~**8**~~***9)*** as an outpatient ~~**and**~~ ***with*** a dose of the same medication on the day of scheduled study visit (Day 29), administered by study personnel in the clinic, to facilitate efficacy assessments, under double-blind conditions. If the patient is on a BID or TID regimen during Period 2, ~~**then any planned dosing following in-clinic treatment should be completed on Day 29 with tablets dispensed for Period 2, after all scheduled visit assessments are completed**~~***the Day 29 assessments should occur after the same dose that corresponds to when assessments were done on Day 0***. Any unused portion of dispensed drug will be returned to the ~~**pharmacy**~~ **site** before ~~**dispensing drug to begin dosing on Day 30 until Final Safety Asssessment on Day 36**~~***enrolling the patient in the expanded access ptogram and dispensing open-label drug.***

~~Final Safety Assessment (Day 36) (±2 days)~~

~~Patients taking open-label amifampridine phosphate following Study Day 29 visit will return to the study site on Day 36 (±2 days) for a final safety assessment, as described in the Schedule of Assessments in Table 3 and Section 13.~~

On Page 37, on Table 3. Schedule of Events, between IP dispense and Days 22-29

deleted text

X~~m~~

On Page 37, on Table 3. Schedule of Events, IP Administration added and deleted text

IP Administration ~~**n,q**~~***m,p***

On Page 37, on Table 3. Schedule of Events, between IP Administration and Days 1-7, deleted and added

X ~~o~~*n*

On Page 37, on Table 3. Schedule of Events, between IP Administration and Day 8 c

(+1 d), deleted and added

X ~~o~~*n*

On Page 37, on Table 3. Schedule of Events, between IP Administration and Days 9-20, deleted and added

X ~~o~~*n*

On Page 37, on Table 3. Schedule of Events, between IP Administration and Day 21 c (+1 d), deleted and added

~~X~~o*X*n

On Page 37, on Table 3. Schedule of Events, between IP Administration and Days 22-29, deleted and added

X ~~o~~*n*

On Page 38, on Table 3. Schedule of Events, deleted row

~~**Patient video**~~	~~**X**~~		~~**X**~~		~~**X**~~		~~**X**~~	

On Page 38, on Table 3. Schedule of Events, deleted text

~~m**Open-label amifampridine phosphate will be dispensed at the Day 29 visit after all dosing and assessments have been completed for Period 2. Patient to get open-label amifampridine phosphate at the same dose and frequency as at the last run-in visit.**~~

On Page 39, on Table 3. Schedule of Events, deleted text

~~n~~*m* Rescue dose amifampridine phosphate will be available in case of worsening symptoms in children previously well-controlled on the drug during open-label run-in or during stabilization after completion of Sequence I.

~~o~~*n* SAE reporting commences when informed consent is signed. Non-serious adverse event reporting commences on Day 1 of run-in (Section *11*~~1111~~).

~~p~~*o* Stimulated single fiber EMG and Slurp test are optional assessments.

~~q~~*p* It is recommended that doses of IP be taken with food.

~~r~~ *q* Screening and Day 1 visit may be cominbed into a single visit.

On Page 40, on Table 3. Schedule of Events, deleted row

~~**Patient video**~~	~~**X**~~		~~**X**~~

On Page 40, on Table 3. Schedule of Events, deleted column

Follow-Up
Day 36 [c] **(±2 d)**
X
X
X
X
X
X
X

On Page 41, under 10.2.1 Inclusion Criteria, deleted and added text

(~~IRB~~*IRB/IEC/REB*)

On Page 41, under 10.2.1 Inclusion Criteria, added text

~~**5. MFM 20 or 32 score equal or less than 48 or 76, respectively, at Screening.**~~

~~**6. In patients naïve to 3,4-DAP or amifampridine phosphate, improvement of >20% in MFM 20 or MFM 32 scores after open label period of uptitration of dose**~~

~~**7. In patients previously stabilized on 3,4-DAP or amifampridine phosphate, history of meaningful improvement in motor function (in opinion of investigator).**~~

On Page 45, under 10.3.2.1 Product Characteristics and Labeling, deleted text

~~**(Firdapse® 10 mg Tablets)**~~

On Page 46, under 10.3.3 Directions for Administration on Table, deleted and added text

~~**Patient video**~~	~~**after MFM**~~
Sitmulated Single fiber EMG^	after ~~**video**~~***SGI***

*Administration of medication represents Time 0 (minutes)

^***Optional test***

~~**At the end of the MFM testing, the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits.**~~

If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the ~~**video of the patient's face**~~***MFM***.

The dose of amifampridine phosphate will be individually determined by the investigator, within the bounds of a total daily dose of 10 mg to 80 mg, divided into doses taken 2 to 4 times per day ***generally*** taken with food (e.g. breakfast, lunch, dinner, and snack before bed) as prescribed by the investigator, based on optimal neuromuscular benefit (see Table 4).

On Page 49, on Table 5. Medications Prohibited During Study, deleted rows

~~**Immunomodulatory treatment (e.g. IVIG) within 3 weeks before Screening**~~
~~**Plasmapheresis (PE or TPE) within 3 weeks before Screening**~~
~~**Rituximab within 6 months before Screening**~~
Any investigational product (other than amifampridine phosphate) or an investigational medical device within 30 days before Screening

On Page 52, under 10.7 Efficacy Variables, deleted and added text

~~**Patient video**~~	~~**after MFM**~~
Stimulated Single fiber EMG	~~**after video***after MFM*~~
Slurp test, CGI-S and CGI-I	At end of assessments

*Administration of medication represents Time 0 (minutes)

~~**At the end of the MFM testing, the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits.**~~

If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the ~~**video of the patient's face***MFM*~~.

On Page 54, under 10.7.5 Slurp Test, deleted section

~~**10.7.6 Videography**~~

~~**Videography, using standardized technology and equipment, will be used to evaluate patient response. An approximate 20-minute video will be obtained at each protocol specified time point and the patient's head/face area will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits.**~~

On Page 54, under 11.1 Adverse Events, changed text

The study period during which all non-serious AEs will be reported begins after informed consent is obtained and the first administration of study drug through the last visit (Study Day ~~**36**~~ **29**) or at the early termination visit.

On Page 61, under 13.1 Screening Visit, deleted and added text

- ~~**Patient video;**~~
- Stimulated single fiber EMG ***(optional);***

- CGI-S;
- Slurp test ***(optional);***
- Assessment of ~~**AEs/**~~SAEs; and
- Assessment of concomitant medications.

On Page 62, under 13.2 Open-label Run-in, deleted text

Improvement of at least 20% in MFM 20 or 32 is not a requirement for these participants. ~~**They must have not been previously assessed for improvement in subject global impression (SGI) and motor function measure (MFM 20 or 32) scores within 3 months prior to participating in this study to avoid possible testing bias.**~~

On Page 62, under 13.2 Open-label Run-in, deleted and added text

- ~~**Patient video;**~~
- CGI-S;
- CGI-I; and
- Slurp test ***(optional).***

Assessment	**Start Time <u>After</u> Dose* (± 10 minutes unless otherwise specified)**
SGI	40 minutes
MFM 20 or 32	after SGI
~~**Patient video**~~	~~**after MFM**~~
Slurp test, CGI-S and CGI-I	At end of assessments

*Administration of medication represents Time 0 (minutes)

~~**At the end of the MFM testing, the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits.**~~

The site pharmacy will dispense bottles containing ***blinded*** amifampridine phosphate or placebo tablets, depending on the patient's Treatment Sequence assignment, for daily outpatient administration for 7 days (Days 1-7). Administration of blinded study medication

will begin with ~~**the first morning dose on Day 1 of Period 1**~~ ***the next scheduled dose following the Day 0 baseline assessment on open-label medication. (see Section 13.3).***

On Page 63, under 13.3 Period 1, deleted text

~~**On Day 1, patients will begin administration of randomized study medication (amifampridine phosphate or placebo tablets) with the first morning dose.**~~
Administration will be continued on an outpatient basis for a total of 7 days (Days 1-7).

On Page 64, under 13.3 Period 1, deleted and added text

- ~~**Patient video;**~~
- CGI-S;
- CGI-I; and
- Slurp test ***(optional).***

Assessment	Start Time <u>After</u> Dose* (± 10 minutes unless otherwise specified)
SGI	40 minutes
MFM 20 or 32	after SGI
~~**Patient video**~~	~~**after MFM**~~
Stimulated Single fiber EMG	after ~~**video**~~***MFM***
Slurp test, CGI-S and CGI-I	At end of assessments

*Administration of medication represents Time 0 (minutes)

~~**At the end of the MFM testing, the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits**~~.If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the ~~**video of the patient's head area**~~***MFM***.

Open-label amifampridine phosphate will be dispensed at the Day 8 visit for administration during the stabilization period, starting ~~**on Day 9**~~***with the next scheduled dose after Day 8 assessments (see Section 13.4).***

On Page 64 and 65, under 13.4 Re-stabilization Period, deleted and added

- ~~**Patient video;**~~

- CGI-S;
- CGI-I; and
- Slurp test ***(optional).***

Assessment	**Start Time <u>After</u> Dose* (± 10 minutes unless otherwise specified)**
SGI	40 minutes
MFM 20 or 32	after SGI
~~**Patient video**~~	~~**after MFM**~~
Slurp test, CGI-S and CGI-I	At end of assessments

*Administration of medication represents Time 0 (minutes)

~~**At the end of the MFM testing, the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits**~~ The slurp test (optional), CGI-S and CGI-I assessments should be done following completion of the ~~**video of the patient's face**~~***MFM.***

The site will dispense bottles containing amifampridine phosphate or placebo tablets, depending on the patient's Treatment Sequence assignment, for Period 2 (Days 22-28). Administration of blinded study medication will begin with the ***next scheduled dose after Day 21 assessments are completed***~~**first morning dose on Day 22 of Period 2**~~ ***(see Section 13.5).***

On Page 65, under 13.5 Period 2, deleted and added text

~~**On Day 22, p**~~Patients will ~~**begin administration with the first morning dose of the randomized**~~***the blinded*** study medication they did not receive in Period 1. Administration will be continued on an outpatient basis for a total of 7 days (Days 22-28).

Patients will report to the study site on Day 29 (+1 day) and receive a dose of the same study medication they received for the previous 7 days, under the supervision of the study personnel, in order to time the following assessments/procedures in relation to the medication dose.

- Assessment of AEs/SAEs;
- ~~**Abbreviated**~~ ***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;
- Urine pregnancy test in females of childbearing potential only;
- Concomitant medications;
- IP accountability;
- Efficacy assessments, including:
  - MFM 20 or 32;
  - SGI (patient/parent/guardian/caregiver);
  - Stimulated single fiber EMG *(optional);*
  - ~~**Patient video;**~~
  - CGI-S;
  - CGI-I; and
  - Slurp test ***(optional).***

Assessment	**Start Time <u>After</u> Dose* (± 10 minutes unless otherwise specified)**
SGI	40 minutes
MFM 20 or 32	after SGI
~~**Patient video**~~	~~**after MFM**~~
Stimulated Single fiber EMG	after ~~**video**~~***MFM***
Slurp test, CGI-S and CGI-I	At end of assessments

*Administration of medication represents Time 0 (minutes)

~~**At the end of the MFM testing, the patient's face will be evaluated for ptosis, extra-ocular movements, facial strength (i.e. smile, eye closure, puffing cheeks), and speech, as age permits.**~~ If the stimulated single fiber EMG (optional assessment) is not to be performed, then the slurp test (also optional), CGI-S and CGI-I assessments should be done following completion of the ~~**video *MFM* of the patient's head area.**~~

After completion of the above procedures/assessments, patients will be ~~**restored to open-label amifampridine phosphate at the same dose and frequency as established in the run in phase of the study and they will be**~~ eligible for an expanded access program.

On Page 66, under 13.5 Period 2, deleted section

~~**13.6 Safety Follow Up**~~

~~**Patients taking open-label amifampridine phosphate, following Study Day 29 visit, will return to the study site on Day 36 (±2 days) for a final safety assessment, including:**~~

- ~~**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;**~~
- ~~**Urine pregnancy test in females of childbearing potential only; and**~~
- ~~**Concomitant medications;**~~
- ~~**IP accountability.**~~

On Page 66, under 13.6 Early Discontinuation Visit, changed text

~~**13.7**~~ ***13.6*** Early Discontinuation Visit

On Page 66 and 67 under 13.6 Early Discontinuation Visit, deleted and added text

- Stimulated Single fiber EMG ***(optional);***
- ~~**Patient video;**~~
- CGI-S;
- CGI-I; and
- Slurp test ***(optional).***

Appendix 10: Protocol Amendment 5

PURPOSE: The purpose of this amendment is as follows:

To formally remove the videotaping of patients from the protocol, clarify the start and stop times of Periods 1 and 2, blinded medication dosing, and remove the Day 36 visit. The patient is either on a stable dose of amifampridine phosphate or has been titrated over a period of 4 weeks. Also, the patient is observed on open label medication for 2 weeks during the restabilization period. Therefore, the Day 36 visit on open label medication adds no new information to the efficacy or safety profile of amifampridine phosphate and the patient may go directly into the expanded access program.

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

MODIFICATIONS TO PROTOCOL:

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

On Page 1, under Clinical Study Protocol, added text

Date of Amendment 5: 26 June 2017

On Page 32, under 8.4.4 Safety of Amifampridine and Amifampridine Phosphate, added text

Based upon the previous clinical studies involving the use of amifampridine in the treatment of Lambert-Eaton myasthenic syndrome (LEMS), there have been reports of provocation of bronchial asthma, respiratory failure, or respiratory disorder. These events are also part of CMS symptoms; however, the risk may be more likely when the patient has asthma or respiratory disorder as a comorbidity with CMS.

On Page 33, under 8.5 Overall Risks and Benefits, added and deleted text

Risks of of study involvement have been minimized by:

1. Patients entering the study may already be on some formulation of 3,4-diaminopyridine and have demonstrated tolerability or;

2. Patients naïve to the medication are titrated to a tolerable and effective dose with open-label medication, under the observation of the Investigator. Thus, the development of adverse events or lack of efficacy is monitored by the Investigator during the step-wise

titration and study medication dose can be reduced or discontinued at any point in the titration for either safety or lack of efficacy.

The pharmacokinetic half-life of amifampridine phosphate is short (1.8 hours), therefore discontinuation of medication will qickly terminate the effects, and mitigate adverse reactions.

This is a withdrawal study design looking at patient worsening on placebo; which is possible due to the short half-life of amifampridine phosphate. Therefore, patients must demonstrate a level of efficacy during the open-label titration period. This further reduces patient risk, by not continuing an experimental medication in patients who fail to demonstrate a benefit.

During the placebo withdrawal period, patients who deteriorate to a point that the Investigator assess to be lower than their baseline, open-label amifampridine phosphate is provided as to rescue the patient.

Refer to the Firdapse Investigator Brochure (February, 2015) for further ~~**discussion**~~ ***information*** on benefit/risk of amifampridine.

On Page 51, under Table 5. Medications Prohibited During Study added and deleted text

The following medicinal products should be use with caution in patients taking amifampridine phosphate:

Medicinal products known to cause cardiac QT prolongation

Medicinal products known to lower epileptic threshold

Medicinal products with atropinic effects

The concomitant use of amifampridine phosphate and medicinal products with atropinic effects may reduce the effect of both active substances and should be taken into consideration. Medicinal products with atropinic effects include tricyclic anti-depressants, most H1 atropinic anti-histamines, anticholinergic, anti-Parkinson medicinal products, atropinic antispasmodics, disopyramide, phenothiazine neuroleptics and clozapine.

Medicinal products with cholinergic effects

The concomitant use of amifampridine phosphate and medicinal products with cholinergic effects (e.g. direct or indirect cholinesterase inhibitors) may lead to an increased effect of both products and should be taken into consideration.

Non-depolarizing muscle relaxant acting medicinal products

The concomitant use of amifampridine phosphate and medicinal products with non-depolarizing muscle relaxant effects (e.g. mivacurium, pipercurium) may lead to a decreased effect of both products and should be taken into consideration.

Depolarizing muscle relaxant acting medicinal products

The concomitant use of amifampridine phosphate and medicinal products with depolarizing muscle relaxant effects (e.g. suxamethonium) may lead to a decreased effect of both products and should be taken into consideration.

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