CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Placebo-Controlled, Crossover Study to Evaluate the Safety and Efficacy of Amifampridine Phosphate in Ambulatory Patients with Spinal Muscular Atrophy (SMA) Type 3
Protocol Number:	SMA-001
Investigational Product:	Amifampridine phosphate (3,4-diaminopyridine phosphate)
IND/EUDRACT Number:	142044 /2017-004600-22
Indication:	Spinal Muscular Atrophy Type 3
External Support:	Catalyst Pharmaceuticals, Inc.
Development Phase:	Phase 2a
Medical Officer:	Gary Ingenito, MD, PhD
Study Design:	Double-blind, Placebo-controlled, Randomized, Crossover
Dose:	15-80 mg total daily dose or placebo equivalent
Patient Population:	Ambulatory patients with SMA Type 3
Version and Date of Protocol:	Version 1.0 dated 20 November 2017 Version 2.0 dated 12 April 2019 Version 3.0 dated 27 September 2019

1 PROCEDURES IN CASE OF AN EMERGENCY

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2 SYNOPSIS

TITLE OF STUDY: A Randomized, Placebo-Controlled, Crossover Study to Evaluate the Safety and Efficacy of Amifampridine Phosphate in Ambulatory Patients with SMA Type 3
PROTOCOL NUMBER: SMA-001
STUDY SITE: Up to 3 sites
PHASE OF DEVELOPMENT: Phase 2a
STUDY RATIONALE: The purpose of this study is to evaluate the safety, tolerability, and efficacy of amifampridine phosphate in ambulatory patients with SMA Type 3.
OBJECTIVES: **Primary** • To characterize the overall safety and tolerability of amifampridine phosphate compared with placebo in patients with SMA Type 3; and • To assess the clinical efficacy of amifampridine phosphate compared with placebo in ambulatory patients with SMA Type 3 using the Hammersmith Functional Motor Scale Expanded (HFMSE).
Secondary • To assess the clinical efficacy of amifampridine phosphate compared with placebo using the six-minute walk test, timed tests, and individual quality of life (INQoL) and pediatric quality of life inventory (PEDSQoL™) assessments.
STUDY DESIGN AND PLAN: This randomized (1:1), double-blind, placebo-controlled, 2-period, 2-treatment, crossover, outpatient study is designed to evaluate the safety, tolerability and efficacy of amifampridine phosphate in ambulatory patients diagnosed with SMA Type 3. The study is planned to include approximately 12 male and female SMA Type 3 patients. The planned duration of participation for each patient is approximately 2 months, based upon length of dose titration and excluding the screening period, which can last up to 14 days. Patients should only be taking the assigned investigational product (amifampridine phosphate 10 mg tablets or matching placebo tablets), no new therapies are permitted during the study. All patients who sign an informed consent will be screened for eligibility to participate in the study, and those successfully completing screening will have procedures/assessments (see Table 1) completed during Run-in, until an optimized stable dose and frequency of amifampridine phosphate is established. At the end of 7 days on a stable daily dose regimen, the patient must show

≥3-point improvement in HFMSE score to be randomized. On Day 0 (randomization), procedures/ assessments (see Table 1) will be conducted to confirm eligibility for randomization, including a negative urine pregnancy test.

Open-label Run-in

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

Period 1 (Weeks 1 and 2)

Patients who have successfully completed the Open-label Run-in and continue to meet all inclusion/exclusion criteria will be randomized (1:1 ratio) on Day 0 to receive either amifampridine tablets (10 mg as amifampridine phosphate) or placebo tablets for 2 weeks, beginning on Day 0 after assessments have been performed on open-label medication. Test medication will be dispensed by the Catalyst designee, according to the randomization schedule provided. Assessments will be performed weekly, in the clinic, as listed in Table 1.

On the last day of Period 1, patients will be evaluated in the clinic after taking the Period 1 study medication. Any remaining Period 1 medication will be collected and study medication for Period 2 dispensed.

Period 2 (Weeks 3 and 4)

Period 2 begins **after** the patient has taken their dose of Period 1 medication in the clinic and had the evaluations listed for end of Week 2 as listed in Table 1. The Period 2 medication will be the alternate study medication (amifampridine or placebo) which was not administered in Period 1.

Assessments will be performed weekly, in the clinic, as listed in Table 1. At the end of Weeks 3 and 4, patients will be evaluated in the clinic after taking the Period 2 study medication. The end of Week 4 represents the end of the study.

NUMBER OF PATIENTS PLANNED:

Approximately 12 SMA Type 3 ambulatory patients.

CRITERIA FOR INCLUSION AND EXCLUSION:

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

1. Willing and able to provide written informed consent after the nature of the study has been explained and before the start of any research-related procedures.
2. Male or female between the ages of 6 and 50 years.
3. Genetically confirmed diagnosis of SMA Type 3.
4. Able to walk independently for at least 30 meters (objectively measured at screening).
5. Not taking Nusinersen for the treatment of SMA (Nusinersen should be stopped at least 6 months before screening). Salbutamol is permitted only if the dose has been stable during the 6 months before screening.
6. Able to swallow oral medication.
7. Female patients of childbearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG] at Screening); and must practice an effective, reliable contraceptive regimen during the study and for up to 30 days following discontinuation of treatment.
8. Ability to participate in the study based on overall health of the patient and disease prognosis, as applicable, in the opinion of the Investigator; and able to comply with all requirements of the protocol, including completion of study questionnaires.

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

1. Epilepsy and currently on medication for epilepsy.
2. An electrocardiogram (ECG) within 6 months before starting treatment that shows clinically significant abnormalities, in the opinion of the Investigator.
3. Breastfeeding or pregnant at Screening or planning to become pregnant at any time during the study.
4. Treatment with an investigational drug (other than amifampridine), device within 6 months prior to Screening or while participating in this study.
5. Surgery for scoliosis or joint contractures within the previous 6 months.
6. Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the study, poses an added risk for the patient, or confound the assessment of the patient.
7. History of drug allergy to any pyridine-containing substances or any amifampridine excipient(s).
8. Less than a 3-point improvement in HFSME from start of the Open label Run -in period to end of Run-in (Day 0).
9. Uncontrolled asthma.

10. Concomitant use with sultopride.
11. Concomitant use with medicinal products with a narrow therapeutic window.

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

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

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

REFERENCE THERAPY, DOSE, ROUTE, AND REGIMEN:

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

DURATION OF TREATMENT:

Approximately 8 weeks (depending on length of dose titration and excluding up to 14-day screening period). The Run-in phase requires that the patient must be on a stable dose and regimen of amifampridine for the last week of Run-in.

CRITERIA FOR EVALUATION:

Safety:

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

Efficacy:

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

Primary -

- Change from baseline in HFMSE total score;

Secondary -

- Change from baseline in quality of life assessments (INQoL or PEDSQoL™).
- Change from baseline in 6-minute walk test.
- Timed items (rising from floor, rising from a chair, climbing 4 steps, walking 10 meters).

STATISTICAL METHODS:

Sample Size Determination

The sample size for this study is based on clinical considerations related to the epidemiology of the disease, and not on a formal statistical power calculation. The sample size should be representative of a sufficient number of patients to evaluate the study objectives (i.e. safety, tolerability, and evidence of efficacy of amifampridine in the target population). It is anticipated approximately 12 patients will be randomized.

Safety Analysis

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

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

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

Efficacy Analysis

Efficacy analysis will be conducted on 2 datasets:

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

3 TABLE OF CONTENTS

List of In-text Tables

List of In-text Figure

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

6MWT	Six-minute walk test
3,4-DAP	3,4-diaminopyridine
AChR-MG	Acetylcholine receptor Myasthenia Gravis
ADL	Activities of Daily Living
ADME	absorption, distribution, metabolism, and excretion
AE(s)	adverse event(s)
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
ANS	autonomic nervous system
AST	aspartate aminotransferase
ATU	Autorisations Temporaires d'Utilisation Normative
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to infinity
CI	confidence interval
C_{max}	peak plasma concentration
CFB	Change from baseline
CMS	congenital myasthenia syndromes
CNS	central nervous system
CRA(s)	clinical research associate(s)
CRF	case report form
CRO	contract research organization
CYP450	cytochrome P450
DBP	diastolic blood pressure
ECG(s)	electrocardiogram(s)
eCRF	electronic case report form
EFNS	European Federation of Neurological Societies
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hERG	human Ether-à-go-go Related Gene

HFMSE	Hammersmith Functional Motor Scale Expanded
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
INQoL	Individual quality of life
IP	investigational product
IRB	institutional review board
K^+	potassium ion
kg	Kilogram
LEMS	Lambert-Eaton myasthenic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia gravis
mg	Milligram
MI	myocardial infarction
mmHg	millimeters of mercury
MS	multiple sclerosis
NAT	N-acetyl transferase
ng/mL	nanograms per milliliter
NMJ	neuromuscular junction
PEDSQL™	pediatric quality of life inventory
Pgp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
PP	per protocol
QMG	Quantitative myasthenia gravis examination
QT	QT wave
QTc	QT wave corrected for heart rate
REB	research ethics board
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SBP	systolic blood pressure
SMA	spinal muscular atrophy
SMN	Survival motor neuron

SOPs	standard operating procedures
$t_{1/2}$	elimination half-life
TEAE(s)	treatment emergent adverse event(s)
TK	Toxicokinetic
T_{max}	time to reach maximum plasma concentration
US	United States

Definition of Terms:

Investigational Product (IP):

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

5 ETHICS

5.1 Independent Ethics Committee / Institutional Review Board

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

5.2 Ethical Conduct of Study

This study will be conducted in accordance with the following:

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

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

5.3 Patient Information and Informed Consent

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

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

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

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

designee, and the IEC. Catalyst Medical Department (or designee) will be responsible for the timely reporting of SAEs to appropriate regulatory authorities, as required.

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

7 INTRODUCTION

A comprehensive review of amifampridine phosphate is contained in the Investigator Brochure supplied by Catalyst (March 2019). Investigators are to review this document before initiating this study.

7.1 Disease Background

Spinal Muscular Atrophy (SMA), first described in the 1890s, is an autosomal recessive neuromuscular disease characterized by degeneration of alpha motor neurons in the anterior horn of spinal cord, leading to progressive denervation atrophy in the involved skeletal muscles, with weakness and paralysis. The disease is due to defects in the Survival Motor Neuron 1 (SMN1) gene in chromosome 5, with deficiency in the SMN protein, a ubiquitously expressed protein, critical to the health and survival of the motor neurons. Recent studies suggest that, due to the ubiquity of SMN protein, SMA might be a multi-system disorder (Hamilton, 2013). The overall incidence of SMA is about 1:6,000-10,000 live births and approximately one in 50 persons are healthy carriers of a defective SMN1 gene (Ogino, 2002, Lunn and Wang 2008). The disease usually appears early in life and is the leading genetic cause of death in infants and toddlers. In most cases, weakness in the legs appears earlier and is generally greater than weakness in the arms. Muscles controlling feeding, swallowing, and respiratory function (e.g., breathing, coughing, and clearing secretions) may also be affected. The clinical phenotype is classified into four types (1, 2, 3, 4), on the basis of age of onset and maximum motor function achieved (Munsat and Davies, 1992 International SMA consortium meeting. (26-28 June 1992, Bonn, Germany). Even within the same type, clinical severity is highly variable and essentially depends on the number of copies of an alternative gene (SMN2), which may produce a limited amount of functional SMN protein, allowing the survival of a variable number of motor neurons. Type 1 patients usually have two copies of the SMN2 gene, or even one copy only, while most Types 3 and 4 patients have three or four copies (Goulet 2013, Kolb 2015).

SMA Type 1 (Werdnig-Hoffman disease), the most severe form, appears in the first months of life, often with a very rapid course (“floppy baby syndrome”), and is usually lethal before

two years of age. SMA Type 2 also presents very early, before 18 months of age, but symptoms are less severe, and these children are able to sit or even to stand unsupported, although they do not achieve the ability to walk independently. SMA Types 3 and 4 are the least severe forms. In Type 3, symptoms appear after 18 months of age, and severity is highly variable. Many patients have only proximal muscle weakness and can stand and walk independently, sometimes until the late disease stages. Life expectancy is near normal. SMA Type 4 has an adult onset, sometimes after 30 years of age, and muscle weakness, mainly of proximal muscles, is relatively mild and slowly progressing, although loss of independent walking has been rarely reported (Shababi 2014).

SMN protein localized in the presynaptic terminals at the neuromuscular junction (NMJ) (Dombert 2014) and its role in NMJ development has been tested by the failure of the cultured muscle cells derived from SMA patients to cluster acetylcholine receptors (AChRs) at the junction (Arnold 2004). In addition, neurofilament accumulation along with poor terminal arborization in postnatal diaphragm samples of SMA Type 1 have been reported (Kariya 2008). Further evidence for a possible role of abnormal NMJ in human SMA pathology derives from a recent study providing a detailed structural characterization of NMJ defects in SMA fetuses (Martinez-Hernandez 2013); main prenatal defects were abnormal modification of acetylcholine receptor clustering, irregular accumulation and positioning of synaptic vesicles, and atypical nerve terminals in motor endplates of SMA Type 1 samples, whereas SMA Type 2 fetuses were similar to controls.

In SMA mice some findings suggest skeletal muscle fiber disruption, such as increased activity of cell death pathways (Mutsaers 2011), abnormal differentiation in muscle satellite cells, deficient formation of myotubes, and decreased muscle fiber size (Lee 2011; Hayhurst 2012). Interestingly, loss of murine SMN specifically in the skeletal muscle causes muscle necrosis, paralysis, and death (Cifuentes-Diaz 2001).

In addition, restoration of SMN in the mature muscle or increasing the muscle mass through different molecules have limited therapeutic benefits in SMA mice (Gavrilina 2008; Rose 2009; Bosch-Marce 2011), further confirming that NMJ maturation defects and abnormal synapses are the hallmark of SMA pathology (Kariya 2008).

There are also data suggesting fatigue and signs of NMJ dysfunction in SMA patients (Montes 2010; Wadman. 2012; Montes 2014; Pera 2017).

Three-Hz repetitive nerve stimulation showed a decremental compound muscle action potential in around half of SMA Types 2 and 3 patients, indicating an impaired NMJ transmission (Wadman 2012; Pera 2017). Furthermore, fatigue tested through 6MWT and expressed as decreased gait speed between first and last minute, is common in SMA Type 3 patients (Montes 2010; Pera 2017). This 6MWT pattern has not been found in other neuromuscular disorders, hence cannot be attributed to muscle weakness alone.

Based on the results of a randomized, double-blind, placebo-controlled, phase 3 clinical trial in SMA Types 1, nusinersen, is an antisense, intrathecally administered product designed to bind to the SMN2 pre-mRNA and promote inclusion of exon 7 (Finkel, 2017). It has been recently approved for treatment of all SMA types by FDA and European Medicines Agency. Furthermore, gene-replacement therapy using intravenous administration of adeno-associated virus 9 carrying SMN complementary DNA showed promising results in a small cohort of SMA Type 1 patients (Mendell, 2017). However, it is reasonable to assume that a single therapeutic solution may not be sufficient, hence combined treatments acting on different disease aspects may be beneficial.

In summary, recent studies in SMA animal models and SMA patients have shown that the NMJ displays significant structural and functional defects that precede overt disease symptoms, suggesting that impaired NMJ function may contribute to SMA pathogenesis and symptoms. Defects in the NMJ appear to precede degeneration of motor neurons suggesting that abnormal formation and/or maintenance of this structure may be a key event in disease pathogenesis. These defects have been observed at both the pre- and postsynaptic components of the NMJ, which likely contribute to the failure to maintain the NMJ and muscle innervation in mouse models of SMA. Finally, NMJ dysfunction has been also demonstrated in SMA patients, mainly in Type 3 subgroup, contributing to the symptoms associated with the disease.

7.2 Amifampridine

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

cleft (Maddison, 1998a; Maddison, 1998b). The influx of ACh into the presynaptic cleft enhances neuromuscular transmission, providing improved muscle function.

Over the last 25 years, a considerable amount of clinical experience with amifampridine has been gained, which provides a strong body of evidence for its efficacy and safety in the treatment of patients with neurologic disorders, including myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), multiple sclerosis (MS), congenital myasthenia syndromes (CMS), downbeat nystagmus, and amyotrophic lateral sclerosis (ALS). Amifampridine has been recommended as first-line symptomatic treatment for LEMS by the European Federation of Neurological Societies (EFNS) (Skeie, 2006; Skeie, 2010; Lindquist, 2011) and amifampridine 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 and the United States of America. The collective body of data indicates that amifampridine/ amifampridine phosphate (salt form of amifampridine) is well tolerated up to and including 80 mg/day (Firdapse Investigator Brochure, March 2019).

7.3 Nonclinical Studies

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

- Five safety pharmacology studies in central nervous system (rat), respiratory (rat), and cardiovascular (telemeterized dogs, *in vitro* human Ether-à-go-go Related Gene (hERG) and rabbit Purkinje fiber)
- Pharmacokinetics and mass balance in rat and dog
- *In vitro* metabolism in human and animal hepatocytes
- Human hepatic cytochrome P450 (CYP450) inhibition and induction
- Human P-glycoprotein (Pgp) interaction
- Single dose toxicity and toxicokinetic (TK) studies in mouse and rat
- Repeat dose toxicity and TK in rat (28-day, 13-week, and 2-year) and dog studies (28-day and 9-month)
- Reproductive and developmental toxicity in rat and rabbit
- Six *in vitro* and *in vivo* genotoxicity studies

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

7.4 Previous Clinical Studies

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

7.4.1 Amifampridine Phosphate in Healthy Subjects

A Phase 1 study 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 subject was randomized to receive either a single dose (2 × 10 mg tablets) of amifampridine as amifampridine phosphate or amifampridine base on one occasion and received the 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 80% to 125% for bioequivalence. The mean elimination half-life ($t_{1/2}$) values of amifampridine were 1.8 and 1.6 hours for the phosphate free base forms, respectively. Amifampridine peak serum levels (C_{max}) was 64.8 ng/mL for the phosphate form and 57.0 ng/mL for the free base form. Potentially higher solubility 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 the salt and free base forms. The most common AE (25 of 40 AEs) in 12 subjects 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 subject and judged possibly related to amifampridine was abdominal pain (4 events). Flu-like symptoms (5 events) and feeling of discomfort (2 events) were also reported for > 1 subject in the study, however were considered not related to amifampridine treatment.

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

A Phase 1 open-label, randomized, single-dose, 2-treatment, 2-period crossover study in 46 healthy volunteers evaluated whether food consumption significantly affected the bioavailability of amifampridine phosphate tablets (LMS-001).. Each subject received 20 mg amifampridine phosphate on 2 occasions, once fasting and once after consumption of a standard high fat breakfast. Each single 20 mg dose of amifampridine phosphate were administered 6 days apart. The results from this study indicate co-administration with food reduces exposures determined by C_{max} and AUC by approximately 40% and 20%, respectively. 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 AEs occurring in ≥ 10% of subjects were: oral paresthesia (20 subjects; 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 subjects following administration of amifampridine phosphate in the fasted state. 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 metabolic rates, 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).

7.4.2 Efficacy of Amifampridine

A Phase 3, randomized, double-blind, placebo-controlled study (LMS-002) evaluated the efficacy and safety of amifampridine phosphate (30-80 mg total daily dose) versus placebo in patients with LEMS. 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 randomized to amifampridine on Day 1 reported, on average, that they were "pleased" (SGI mean ±SD score of 5.9 ± 1.2) while on treatment. 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 (free 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 discontinuation of amifampridine in a double blind controlled manner led to recurrence of underlying symptoms. Refer to the Firdapse Investigator Brochure (March 2019) for further details on these studies.

7.4.3 Safety of Amifampridine and Amifampridine Phosphate

Safety data collected from 1,454 patients or healthy volunteers in various studies (e.g. controlled study LMS-002, other 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, March 2019). The most common AEs 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. Ten of 1454 (0.69%) individuals exposed to amifampridine experienced seizures. Electroencephalogram (EEG) findings, reported for 3 of the 10 patients, did not show epileptiform activity. Three of 10 seizures occurred in patients with LEMS (3/209; 1.44%), 4 occurred in patients with MS (4/774; 0.5%), 1 occurred in a patient with CMS (1/88; 1.14%) (Harper, 2000) and 2 seizures were reported in a literature-based study where both MG and LEMS patients were enrolled, but the paper did not state the indication (Sanders, 1993; Sanders, 2000; Flet, 2010; McEvoy, 1989; Boerma, 1995; Bever, 1996).

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

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

7.4.4 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 salt forms) at doses up to 80 mg per day. Current data demonstrate that amifampridine phosphate has an acceptable tolerability profile with a positive risk-benefit in patients treated with amifampridine. Refer to the Investigator Brochure (March 2019) for further discussion on benefit/risk of amifampridine.

7.4.5 Study Rationale

As discussed above in Section 7.4, a considerable amount of clinical experience is available with amifampridine and, in December 2009, amifampridine phosphate tablets (10 mg as free base), received marketing approval by the European Commission as Firdapse® for the symptomatic treatment of patients with LEMS. Case reports, animal data suggest that amifampridine may also have clinical utility in patients with SMA Type 3, providing

symptomatic relief through its action on the impaired NMJ transmission. Thus, the purpose of this study (SMA-001) is to demonstrate the safety and efficacy of amifampridine in patients with Type 3 SMA.

8 STUDY OBJECTIVES

8.1.1 Primary Objectives

The primary objectives of the study are:

- To characterize the overall safety and tolerability of amifampridine compared with placebo in patients with SMA Type 3; and
- To assess the clinical efficacy of amifampridine compared with placebo in ambulatory patients with SMA Type 3 based on change from baseline in the Hammersmith Functional Motor Scale Expanded (HFMSE) scores.

8.1.2 Secondary Objective

The secondary objective of the study is:

- To assess the clinical efficacy of amifampridine compared with placebo by using the change from baseline in six-minute walk test, timed tests, and quality of life assessments;

9 INVESTIGATIONAL PLAN

9.1.1 Overall Study Design and Plan

This is a stratified, randomized (1:1), double-blind, placebo-controlled, , 2-treatment, 2-sequence, crossover , outpatient study designed to evaluate the safety, tolerability and efficacy of amifampridine in ambulatory patients diagnosed with SMA Type 3. The study will include about 12 male and female SMA Type 3 patients,

The planned duration of participation for each patient is at least 60 days excluding the screening period, which can last up to 14 days.

All patients who sign an informed consent will be screened for eligibility to participate in the study: inclusion and exclusion criteria; medical and medication history; complete physical exam (including height, weight); vital signs; standard 12-lead ECG, including QTc evaluation; clinical laboratory testing; serum pregnancy testing (females of childbearing potential only; result must be negative to proceed into the run-in period with open-label IP

administration); confirmed molecular diagnosis of SMA; and assessment of serious adverse events (SAEs) (Table1)

Those patients successfully completing screening will have procedures/assessments (see Table 1 Schedule of Events) conducted at the start of the Run-in period (Day 1, before starting medication) and during Run-in, until stable dose and frequency of amifampridine is established for at least 7 days, and at least a 3-point improvement in HFMSE score is achieved. Screening and the start of the Run-in period may be combined into a single visit, in which case overlapping procedures/assessments will only need to be performed once. On the last day of the Run-in period (Day 0), procedures/assessments, as detailed in Table 1 will be conducted to confirm eligibility for randomization, including a negative pregnancy test. Every attempt should be made to have the same individual perform all assessments for a patient throughout the study.

Randomized patients will be assigned to one of 2 treatment sequences under double-blind conditions, either placebo or amifampridine phosphate in Part 1, and then cross-over in Part 2 to receive the alternate medication which was not taken in Part 1.

Open-label Run-in

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

Randomization

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

Period 1 (Days 1-14) (±1 day for each of Days 7 and 14)

Patients who have successfully completed the Open-label Run-in and continue to meet all inclusion/exclusion criteria will be randomized (1:1 ratio) on Day 0 to receive either

amifampridine tablets (10 mg as amifampridine phosphate) or placebo tablets for 14 days, under double-blind conditions, (blinded medication to start after assessments obtained on open-label medication, on Day 0). Test medication will be dispensed by the Catalyst designee, according to the randomization schedule provided by Sponsor. All unused medication and the container must be brought back to the study site at each clinic visit. Safety and efficacy assessments will be made, in the site clinic, on Days 7 and 14 as detailed in the Schedule of Assessments in Table 1 and Section 12 STUDY Procedures.

Period 2 (Days 15-28) (±1 day for each of Days 21 and 28)

Following the in-clinic assessments on Day 14 of Period 1, the Period 1 study medication is collected and the patient should be given the blinded Period 2 medication; either amifampridine phosphate or placebo tablets (whichever they did not receive in Period 1) for 14 days. The Period 2 medication is to start with the next dose after the assessments are performed on Day 14 with Period 1 medication.

Safety and efficacy assessments will be made, in the site clinic, on Days 21 and 28 as detailed in the Schedule of Assessments in Table 1 and Section 12 STUDY Procedures. All unused medication and the container must be brought back to the study site at each clinic visit, including on Day 28, which represents the end of the study.

Table 1 Schedule of Events

Study Assessment or Event [b]	Screening	Run-in			Period 1		Period 2	
		Start [a]		Last Visit				
	Days -14 to -1	Day 1	Week 3	Day 0 end of Run-in	Day 7 ±1 day	Day 14 ±1 day	Day 21 ±1 day	Day 28 ±1 day
Informed consent [c]	X							
Inclusion/Exclusion Criteria	X			X				
Randomization				X				
Medical history	X							
Complete physical exam	X			X				X
Vital signs	X		X	X	X	X	X	X
12-Lead ECG and QTc evaluation	X			X				X
Clinical laboratory tests [d]	X			X				X
Pregnancy test [e]	X			X		X		X
Dispense blinded IP [f,g]				X		X		
IP accountability			X	X	X	X	X	X
Able to walk 30 meters	X							
INQoL or PEDSQL				X	X	X	X	X
HFMSE	X	X		X	X	X	X	X
Six-minute walk test				X	X	X	X	X
Time to rise from floor				X	X	X	X	X
Time to rise from chair				X	X	X	X	X
Time to climb 4 stairs				X	X	X	X	X
Time to walk 10 meters				X	X	X	X	X
Adverse events/SAEs [h]	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Patient Dosing Diary Provided		X	X	X	X	X	X	

ECG = electrocardiogram; HFSME= Hammersmith Functional Motor Scale Expanded; IP = investigational product (amifampridine or placebo); INQoL = individual quality of life; PEDSQL = pediatric quality of life inventory; SAE = serious adverse event. *Footnotes continue on next page.*

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

[b] All safety assessments (vital signs, ECGs, laboratory tests) are to be performed before the dose taken in the study clinic unless specified otherwise. All efficacy assessments will be performed at standardized times relative to the dose that must be taken in the study clinic on Days 0, 7, 14, 21, and 28 according to the efficacy assessments schedule in Section 9.7.

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

[d] Clinical laboratory tests include serum chemistry, hematology, and urinalysis.

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

[f] IP will be administered by the clinic staff during in-clinic visit so assessments can be timed according to IP administration.

[g] Patients will be provided blinded packages containing amifampridine or placebo depending on their randomized sequence of treatment. Collect all open-label medication.

[h] SAE reporting commences when informed consent is signed. Non-serious adverse event reporting commences on Day 1 of run-in (Section 10).

9.2 Selection of Study Population

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

9.2.1 Inclusion Criteria

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

1. Willing and able to provide written informed consent after the nature of the study has been explained and before the start of any research-related procedures.
2. Male or female between the ages of 6 and 50 years.
3. Genetically confirmed diagnosis of SMA Type 3.
4. Able to walk independently for at least 30 meters (objectively measured at screening).
5. Not taking Nusinersen for the treatment of SMA (Nusinersen should be stopped at least 6 months before the screening). Salbutamol is permitted only if the dose has been stable for 6 months before screening.
6. Able to swallow oral medication.
7. Female patients of childbearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG] at screening); and must practice an effective, reliable contraceptive regimen during the study and for up to 30 days following discontinuation of treatment.
8. Ability to participate in the study based on overall health of the patient and disease prognosis, as applicable, in the opinion of the Investigator; and able to comply with all requirements of the protocol, including completion of study questionnaires.

9.2.2 Exclusion Criteria

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

1. Epilepsy and currently on medication.
2. An electrocardiogram (ECG) within 6 months before starting treatment that shows clinically significant abnormalities, in the opinion of the Investigator.
3. Breastfeeding or pregnant at Screening or planning to become pregnant at any time during the study.
4. Surgery for scoliosis or joint contractures within the previous 6 months.
5. Treatment with an investigational drug (other than amifampridine) or device within 6 months before Screening or while participating in this study.
6. Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the study, poses an added risk for the patient, or confound the assessment of the patient.
7. History of drug allergy to any pyridine-containing substances or any amifampridine excipient(s).
8. Less than 3-point improvement in HFMSE from start to end of Run-in period.
9. Uncontrolled asthma.
10. Concomitant use with sultopride.
11. Concomitant use with medicinal products with a narrow therapeutic window.

9.2.3 Removal of Patients from Treatment or Assessment

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

Catalyst must be notified of all patient withdrawals from the study or from treatment with IP as soon as possible. Catalyst also reserves the right to discontinue the study at any time for

either clinical or administrative reasons and to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance.

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

- Patient experiences a serious or intolerable AE;
- Patient requires medication prohibited by the protocol;
- Patient becomes pregnant (refer to Section 10.4 Pregnancy for details on the reporting procedures to follow in the event of pregnancy).
- Patient does not adhere to study requirements specified in the protocol;
- Patient was erroneously admitted into the study or does not meet inclusion criteria;
- Patient is lost to follow-up.

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

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

9.2.4 Patient Identification

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

9.2.5 Re-screening

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

Clinical laboratory tests do not have to be repeated for 30 days, except for pregnancy test. Patients may be replaced if discontinued from the study after randomization.

9.3 Treatments

9.3.1 Treatments Administered

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

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

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

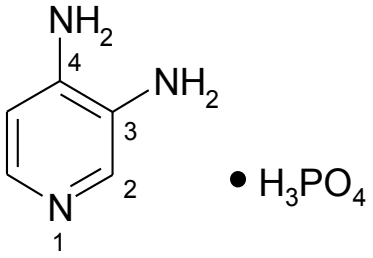
9.3.2 Identity of Investigational Product

The chemical name of amifampridine phosphate is:

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

The chemical structure is provided in Figure 1.

Figure 1. Chemical Structure of Amifampridine Phosphate



9.3.2.1 Product Characteristics and Labeling

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

The tablets of amifampridine and placebo are to be dispensed by the Catalyst designee into suitably sized pharmacy containers for patient use. Each bottle provided to patients will be labeled to include the compound name (Open-label or study drug, depending on the study period), site number, patient ID number, date dispensed, storage instructions, the statement 'Caution – New Drug – Limited to investigational use', trial number, manufacturer name and address, and instructions for use. Any additional regional label requirements and translations will be included in accordance with local regulations.

9.3.2.2 Storage

At the study site, all IP must be stored under the conditions specified, 20-25° Celsius (C) (excursions between 15-30° may be allowed) and in a secure area accessible only to the pharmacist and clinical site personnel. All IP must be stored and inventoried, and the inventories must be carefully and accurately documented according to applicable national and local regulations, ICH GCP, and study procedures.

9.3.3 Directions for Administration

All doses of study treatment will be taken at home, except one of the doses on the day of the in-clinic study visits, when it will be administered by study personnel and will be administered in the clinic to facilitate timing of efficacy assessments. Test medication should be taken every day at approximately the same time, at the dose and frequency instructed by Investigator. On the day of an in-clinic study visit (Days 0, 7, 14, 21, and 28), dose administration will be the medication the patient has been taking for the previous days, but administered by the study personnel 45 minutes before the first efficacy assessment. If the patient takes the dose three times a day, the patient should be given specific instructions on dosing relative to the time of their visit to assure a dose will be given during the in-clinic visit within the required time window. All safety assessments will be performed before the dose is administered to the patient during the in-clinic visit. Efficacy assessment will be performed at standardized times relative to the dose administered in the clinic.

Assessment	Start Time After Dose (+ 10 minutes unless otherwise specified)
HFSME	**45 minutes**
6-minute walk test	After HFSME
Time to rise from floor	After 6-minute walk
Time to rise from chair	After rise from floor
Time to climb 4 stairs	After rise from chair
Time to walk 10 meters	After climb stairs
Quality of Life Assessment	After 10-meter walk

The dose of amifampridine will be individually determined by the Investigator, within the bounds of a total daily dose of 15 mg to 80 mg, divided into doses taken 3 to 4 times per day as prescribed by the Investigator, based on optimal neuromuscular benefit. The maximum single dose is 20 mg. Amifampridine dose will be titrated upward every 3 to 4 days, starting at 15 mg/day, at the discretion of the Investigator. Pediatric dosing guidelines are presented in Table 2.

Table 2 Pediatric Dosing Guidelines

	Ages 6 to 16 Years	Ages >16 years
Recommended starting dose	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 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 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	80 mg/day

Patients will either visit or have telephone/video contact with the site for each dose titration and at least one in-person site evaluation at Week 3 of the Run-in period. When the Investigator determines that the patient has reached the maximal tolerable dose, the patient should demonstrate they can remain on a stable dose and frequency for at least an additional 7 days. The Open-label Run-in period may be extended if additional time is needed for dose

titration. At the end of this period, patients must show a ≥3-point improvement in HFMSE from start of Run-in, to be eligible for randomization (Day 0).

9.3.4 Method of Assigning Patients to Treatment Groups

Patients will be randomized on the last day of the open-label run-in period (Day 0), in a 1:1 ratio, to 1 of 2 treatment sequences (amifampridine for Period 1 and placebo for Period 2 or placebo for Period 1 and amifampridine for Period 2. IP will be administered under double-blind conditions. Randomized patients who discontinue after initiation of treatment may be replaced.

The randomization code will be provided to the unblinded Catalyst designee. Details will be included in the Pharmacy Manual.

9.3.5 Selection of Doses Used in the Study

Amifampridine is given in 3 or 4 divided doses, with no single dose >20 mg and the maximum daily dose of 80 mg. Safety of a single maximum dose of 20 mg is based on completed animal and *in vitro* pharmacology, PK, and toxicology studies. Previous studies with amifampridine in this dose range have shown clinical benefit in other neurologic disorders (LEMS, MG).

9.3.6 Blinding

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

9.3.7 Treatment Compliance

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

9.3.8 Investigational Product Accountability

The study site staff 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 and the study site staff must retain all unused or expired study supplies until the study monitor (on-site CRA) has confirmed the accountability data.

9.3.9 Return and Disposition of Clinical Supplies

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

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

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

9.4 Prior and Concomitant Medications

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

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

Medications that are contraindicated when combined with amifampridine phosphate are:

- Medicinal products with narrow therapeutic window
- Sultopride

Amifampridine phosphate should be used with caution when combined with the following products:

- Medicinal products known to lower the epileptic threshold

- Medicinal products with atropinic effects
- Medicinal products with cholinergic effects
- Non depolarizing muscle relaxant acting medicinal products
- Depolarizing muscle relaxant acting medicinal products.

Medications prohibited during the study are listed in Table 3.

Table 3. Medications Prohibited During Study

Nusinersen must be stopped at least 6 months before screening. Salbutamol, is permitted only if the dose has been stable for 6 months before screening.
Any investigational product (other than amifampridine) or an investigational medical device within 6 months before Screening.
Medications that are contraindicated when combined with amifampridine phosphate are: • Medicinal products with narrow therapeutic window • Sultopride
Amifampridine phosphate should be used with caution when combined with the following products: • Medicinal products known to lower the epileptic threshold • Medicinal products with atropinic effects • Medicinal products with cholinergic effects • Non depolarizing muscle relaxant acting medicinal products • Depolarizing muscle relaxant acting medicinal products.

9.5 Dietary or Other Protocol Restrictions

9.5.1 Dietary Restrictions

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

9.5.2 Contraception

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

9.6 Safety Variables

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

9.6.1 Adverse Events

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

9.6.2 Vital Signs

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

9.6.3 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 1 Schedule of Events for the tests required by Protocol. The scheduled clinical laboratory tests are listed in Table 4. All abnormal clinical laboratory test 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 4 Clinical Laboratory Tests

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

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

9.6.4 Pregnancy Testing

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

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

9.6.5 Electrocardiogram (ECG)

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

9.6.6 Physical Examination

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

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

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

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

9.7 Efficacy Variables

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

Assessment	**Start Time After Dose (+ 10 minutes unless otherwise specified)**
HFSME	**45 minutes**
6-minute walk test	After HFSME
Time to rise from floor	After 6-minute walk
Time to rise from chair	After rise from floor
Time to climb 4 stairs	After rise from chair
Time to walk 10 meters	After climb stairs
Quality of Life Assessment	After 10-meters walk

9.7.1 Hammersmith Functional Motor Scale Expanded (HFSME)

The HFSME (Appendix 1) assess motor function (e.g. lying, rolling, sitting, crawling, attaining standing, walking, running, and jumping) in order of progressive difficulty, with higher values showing higher function abilities. The HFSME was expanded from the original 20-item Hammersmith functional motor scale by incorporating 13 relevant items to eliminate the "ceiling" effect of the original scale when applied to ambulant SMA patients. Each item scores 2 for unaided, 1 for assistance, and 0 for inability. A total score is calculated by summing the scores of the individual items. The total score can range from 0 (all activities failed) to 66 (all activities achieved unaided). The HFSME shows good test-retest reliability and correlation with other clinical measures in SMA, especially in Type 3 (Montes, 2015).

9.7.2 6-minute walk test

This is a test of endurance which has been validated for ambulant patients with SMA (Montes, 2010). Participants are instructed to walk as fast as possible along a 25-meter linear marked course for 6 minutes. Meters walked are recorded.

9.7.3 Timed items

- Rising from floor – the time required in rising from the supine position

- Rising from a chair – the time required to stand from a seated position
- Climbing 4 steps – the time required to climb 4 standardized steps
- Walking 10 meters – the time required to walk 10 meters as fast as possible

9.7.4 Quality of life assessment

The Individualized Quality of Life for neuromuscular disease (INQoL) or the Pediatric Quality of Life (PEDSQL™) will be assessed for adult or pediatric patients, respectively. Each QoL evaluation is available in the local language for the appropriate sites.

10 Reporting Adverse Events

10.1 Adverse Events

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

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

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

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

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

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

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

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

Table 5 Categories of Severity for Adverse Events

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

Activities of Daily Living (ADL)

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

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

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

Table 6 Description of Relationship to Adverse Event Categories

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

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

10.2 Serious Adverse Events

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

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

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

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

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

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

For some SAEs, Catalyst and/or designee 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 and CRO 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 IEC will be done in compliance with the standard operating procedures and policies of the IEC and with applicable regulatory requirements. Adequate documentation must be provided showing that the IEC was properly and promptly notified as required.

10.3 Safety Blood Collection

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

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

10.4 Pregnancy

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

10.5 Urgent Safety Measures

The regulations governing clinical trials state that the sponsor and Investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC, "…in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the Investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IEC 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 to the Sponsor or designee 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.

10.6 Medical Monitor Contact Information

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.

Stanley Iyadurai, MD, PhD
Vice President, Clinical Affairs
Catalyst Pharmaceuticals, Inc.
Tel: +1 305-420-3239

Email: siyadurai@catalystpharma.com

11 APPROPRIATENESS OF MEASUREMENTS

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

12 STUDY PROCEDURES

12.1 Screening Visit

An ICF must be signed and dated by the patient and parents for patients with age < 18 years, the Investigator or designee, and witness (if required) before any study-related procedures are performed. Refer to Section 9.4 for prohibited medications.

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

- Informed Consent;
- Inclusion/Exclusion criteria;
- Demographics (sex, race, ethnic origin, age);
- Medical history, including allergy history;
- Standard resting 12-lead ECG;
- Complete physical examination including weight and height;
- Vital signs (seated position), including SBP, DBP, heart rate, respiration, and body temperature;
- Clinical laboratory tests including hematology, chemistry, and urinalysis;
- Serum pregnancy test in females of childbearing potential only;
- HFSME;
- Walk 30 meters;
- SAEs;
- Concomitant medications.

12.2 Open-label Run-in

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

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

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

12.3 Period 1

12.3.1 Day 0

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

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

Order of Assessment at Each Study Visit (when applicable)	Start Time After Dose (+ 10 minutes unless otherwise specified)
HFSME	**45 minutes**
6-minute walk test	After HFSME
Time to rise from floor	After 6-minute walk
Time to rise from chair	After rise from floor
Time to climb 4 stairs	After rise from chair
Time to walk 10 meters	After climb stairs
Quality of Life Assessment	After 10-meters walk

- INQoL for neuromuscular disease or the PEDSQL™ assessments will be completed for adult or pediatric patients, respectively after the six other assessments have been made.
- Randomization to Treatment Sequence

All open-label IP should be collected from the patient. The Investigator will dispense bottles containing amifampridine or placebo tablets, depending on the patient's randomization assignment, for daily outpatient administration for 14 days (Days 1-14), starting after completion of all assessments on Day 0.

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

Patients continue administration of blinded study medication (amifampridine or placebo) until the Day 14 visit.

12.3.2 Period 1, Days 7 and 14 (or Early Termination Visit)

Patients will report to the study site on Days 7 and 14 (±1 day) and have the assessments/procedures listed below completed. Study personnel will administer a dose of the patient's blinded medication at the clinic on Days 7 and 14, so assessments can be performed according to the specified times in relation to the time of dose administration. The medication administered by study personnel should be the same as what the patient has been taking for Period 1. If the patient is taking study medication 3 or 4 times a day, the visit needs to be arranged such that one of the doses is administered by the study site personnel, and assessments should occur after the same dose each visit.

- Assessment of AEs/SAEs;
- Vital signs (seated position), including SBP, DBP, heart rate, respiration, and body temperature;
- Urine pregnancy test in females of childbearing potential (only on Day 14);
- Concomitant medications;
- Collect patient Drug Dosing Diary and perform IP accountability (a new Drug Dosing Diary is given to the patient on Days 7 and 14);
- Efficacy assessments following in-clinic dose of double-blind medication as listed below:

Order of Assessment at Each Study Visit (when applicable)	**Start Time After Dose (+ 10 minutes unless otherwise specified)**
HFSME	**45 minutes**
6-minute walk test	After HFSME
Time to rise from floor	After 6-minute walk
Time to rise from chair	After rise from floor
Time to climb 4 stairs	After rise from chair
Time to walk 10 meters	After climb stairs
Quality of Life Assessment	After 10-meters walk

- INQoL for neuromuscular disease or the PEDSQL™ assessments will be completed for adult or pediatric patients, respectively after the six other assessments have been made.

On Day 14, all Period 1 study medication should be collected after the assessments have been performed, and study medication for Period 2 dispensed. The first dose of Period 2 medication is to be administered after the assessments are completed and at the time of the next regularly scheduled dose.

12.4 Period 2, Days 21 and 28 (or Early Termination Visit)

Patients will report to the study site on Days 21 and 28 (±1 day) and have the assessments/procedures listed below completed. Study personnel will administer a dose of the patient's blinded medication at the clinic on Days 21 and 28, so assessments can be

performed according to the specified times in relation to the time of dose administration. The medication administered by study personnel should be the same as what the patient has been taking for Period 2. If the patient is taking study medication 3 or 4 times a day, the visit needs to be arranged such that one of the doses is administered by the study site personnel.

- Assessment of AEs/SAEs;
- Complete physical exam (Day 28 only);
- Vital signs (seated position), including SBP, DBP, heart rate, respiration, and body temperature;
- 12-lead ECG (Day 28 only);
- Clinical laboratory tests (Day 28 only);
- Urine pregnancy test in females of childbearing potential (Day 28 only);
- Concomitant medications;
- Collect patient Drug Dosing Diary and perform IP accountability (a new Drug Dosing Diary is given to the patient on Day 21);
- Efficacy assessments following in-clinic dose of double-blind medication as listed below:

Order of Assessment at Each Study Visit (when applicable)	**Start Time After Dose (+ 10 minutes unless otherwise specified)**
HFSME	**45 minutes**
6-minute walk test	After HFSME
Time to rise from floor	After 6-minute walk
Time to rise from chair	After rise from floor
Time to climb 4 stairs	After rise from chair
Time to walk 10 meters	After climb stairs
Quality of Life Assessment	After 10-meters walk

- INQoL for neuromuscular disease or the PEDSQL^{TM} assessments will be completed for adult or pediatric patients, respectively after the six other assessments have been made.

On Day 28, all Period 2 study medication should be collected after the assessments have been performed. This represents the end of the study.

13 DATA QUALITY ASSURANCE

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

At visits during and after the study, a CRA will monitor the site for compliance with regulatory documentation, with a focus on accurate and complete recording of data on CRFs from source documents, adherence to protocol, randomization AE/SAE reporting, and drug accountability records.

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

14.1.1 Interim Analyses

No interim analyses are planned.

14.2 Analysis Populations

The following analysis populations will be defined for the study:

- Safety Population: The safety population will consist of all subjects who are enrolled in the study and have received at least one dose of amifampridine and includes subjects who begin the Run-in period regardless of whether they are randomized to double blind medication on Day 0.
- Full Analysis Set (FAS): This population consists of all randomized subjects who receive at least 1 dose of IP (amifampridine or placebo) and have at least one post-treatment efficacy assessment. Subjects will be compared for efficacy according to the treatment to which they were randomized, regardless of the treatment actually received.
- Per Protocol (PP): This population is a subset of the FAS population, excluding subjects with major protocol deviations. The PP population will include all FAS subjects who:

- Have no major protocol deviations or inclusion/exclusion criteria deviations that might potentially affect efficacy, and
- Subjects who took at least 80% of the required treatment doses.
- The PP population will be determined before database lock and unblinding subject treatment codes.

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

14.3 Primary Endpoint

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

14.4 Secondary Endpoints

The secondary efficacy endpoints of the study are:

- the six-minute walk test
- timed tests
- quality of life assessments

14.5 Safety Analysis

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

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

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

low/high, high/low, high/normal, and high/high. Similar shift tables will also be constructed for physical exam results. ECG results will be summarized in a shift table with the following shifts presented: normal/normal, normal/abnormal, abnormal/normal and abnormal/abnormal. A table of descriptive statistics for QTc interval by treatment, day and period will be created.

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

14.6 Efficacy Analysis

14.6.1 Primary Efficacy Endpoint Analyses

The change-from-baseline scores [Change From Baseline $(CFB)_7 = HFMSE_7 – HFMSE_0$, $CFB_{14} = HFMSE_{14} – HFMSE_0$, $CFB_{21} = HFMSE_{21} – HFMSE_0$, $CFB_{28} = HFMSE_{28} – HFMSE_0$] will be analyzed using a mixed effects linear model. Treatment (amifampridine (A) or placebo (P)) and Sequence (A/P or P/A) and the Treatment by Sequence interaction will enter the model as fixed effects. Subject within Sequence will enter the model as a random effect with a block diagonal covariance structure. Population marginal means[1] will be estimated for each of the four Period and Sequence combinations.

Other analyses may be carried out as specified in the Statistical Analysis Plan.

14.6.2 Secondary Efficacy Endpoint Analyses

The quantitative secondary efficacy endpoints (6-minute walk test, Time-to-rise-from-floor, Time-to-rise-from chair, Time-to-climb-4-stairs, and Time-to-walk-10 meters) will be analyzed as the HFSME is analyzed. The four CFB scores will be analyzed with a linear mixed model. Treatment and Sequence will be entered as fixed effects. Subject within Sequence will be entered as a random effect with a block-diagonal covariance structure. Population marginal means will be estimated for each of the four Period and Sequence combinations.

Results from INQoL questionnaires and PEDSQL™ inventory of disease specific symptoms will be summarized with descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) per time point (Days 0, 7, 14, 21, and 28) and CFB, using the Day 0

[1] Also known as “LSMEANS”.

response as the baseline level). The subscales of the QoL questionnaires will be similarly summarized.

14.7 Determination of Sample Size

The sample size for this study is based on clinical considerations related to the epidemiology of the disease, and not on a formal statistical power calculation. The sample size should be representative of a sufficient number of patients to evaluate the study objectives (i.e. safety, tolerability, and evidence of efficacy of amifampridine in the target population). It is anticipated approximately 12 patients will be randomized.

14.8 Changes in the Conduct of the Study or Planned Analyses

Any change in study conduct considered necessary by the Investigator will be made only after consultation with Catalyst., who will then issue a formal protocol amendment to implement the change. The only exception is when an Investigator considers that a patient's safety is compromised without immediate action.

Protocol amendments that influence patient risk or the study objectives, or require revision of the ICF, must receive approval from the IEC prior to their implementation.

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

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

15 COMPENSATION, INSURANCE, AND INDEMNITY

There will be no charge to study patients to be in this study. Catalyst will pay all costs of tests, procedures, and treatments that are part of this study (as included in the site budget). In addition, after IEC 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. 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.

16 CASE REPORT FORMS AND SOURCE DOCUMENTS

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

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

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

In the application, study data on the eCRFs will be verified to the source data, which necessitates access to all original recordings, laboratory reports, and patient records. In addition, all source data should be attributable (signed and dated). The Investigator must therefore agree to allow direct access to all source data. Patients must also allow access to their medical records, and patients will be informed of this and will confirm their agreement when giving informed consent. The Investigator must review and electronically sign the completed eCRF casebook to verify its accuracy. A CRA designated by Catalyst will compare the eCRFs in the application with the original source documents at the study site and evaluate them for completeness and accuracy before designating them as "Source Data Verified" in the application. If an error is discovered at any time or a clarification is needed, the Data Manager, CRA, or designee, will create an electronic query on the associated field. Site personnel will then answer the query by either correcting the data or responding to the

query. The Data Manager or CRA will then review the response and determine either to close the query or re–query the site if the response does not fully address the question. This process will be repeated until all open queries are answered and closed.

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

17 STUDY MONITORING AND AUDITING

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

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

18 RETENTION OF RECORDS

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

All study records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until (1) there are no pending or contemplated marketing applications in an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The Investigator/institution should retain patient identifiers and records for at least 15 years after the completion or discontinuation of the study. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by a Catalyst agreement. Catalyst must be notified and will assist with retention should Investigator/institution be unable to continue maintenance of patient files. It is the responsibility of Catalyst to inform the Investigator /institution as to when these documents no longer need to be retained.

19 USE OF INFORMATION AND PUBLICATION

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

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21 INVESTIGATOR RESPONSIBILITIES

21.1 Conduct of Study and Protection of Human Patients

The Investigator will ensure that:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients that the drug is being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in compliance with ICH E6 (Section 4.8), and other applicable local regulations, are met.
- He or she will report to the sponsor adverse experiences that occur during the investigation in compliance with the standard operating procedures and policies of the EC and with applicable regulatory requirements.
- He or she has read and understands the information in the Investigator 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 IEC 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 IEC. Additionally, he or she will not make any changes in the research without IEC approval, except where necessary to eliminate apparent immediate hazards to human patients.
- He or she agrees to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent ICH and GCP requirements.
- He or she agrees to comply with electronic signature requirements in accordance with ICH requirements and applicable laws and local regulations.

22 SIGNATURE PAGE

Protocol Title:

A Randomized, Placebo-Controlled, Crossover Study to Evaluate the Safety and Efficacy of Amifampridine Phosphate in Ambulatory Patients with Spinal Muscular Atrophy (SMA) Type 3

Protocol Number: SMA-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.

Stanley Jan Brunk 27 Sep 2019

Medical Monitor Signature Date

Printed name: Stanley Iyadurai, MD, PhD
Vice President, Clinical Affairs
Catalyst Pharmaceuticals, Inc.

Appendix 1 : Hammersmith Functional Motor Scale for SMA

Smartnet & PNCR — **Hammersmith Functional Motor Scale for SMA (HFMS)** — 07/03/09

Name — DOB

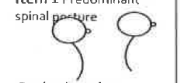
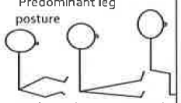
Date of assessment — Time taken to complete

Date of spinal surgery — Evaluator

Please circle highest current level of independent mobility — LBC = Limited by contracture

None — Rolls — Bottom shuffles — creeps /crawls — Walks with crutches / frame /rollator — Walks with KAFO's / AFO's — Independent walking

Comment.....

Test	Instruction	2	1	0	L B C	S =	Comments S = score
1 Plinth /chair sitting Can be over edge of plinth or on plinth / floor. Record best you see	*Can you sit on the plinth /chair without using your hands for support for a count of 3?(Back unsupported /feet +/- support)*	Able to sit using no hand support for a count of 3 or more	Needs one hand support to maintain balance for a count of 3	Needs two hand support to maintain balance Unable to sit			Item 1 Predominant spinal posture  Predominant leg posture  Circle predominant spinal posture and leg position
2 Long sitting Legs straight = knees maybe flexed, knee caps pointing upwards, ankles <10cm apart	*Can you sit on the floor/plinth without using your hands for support and with your legs straight for a count of 3?*	Able to sit on floor/plinth with legs straight without hand support for a count of 3	Able to sit on floor/plinth with legs straight propping with one hand support for a count of 3	Able to long sit using two hands for a count of 3 Or unable to sit with straight legs			
3 One hand to head in sitting Hand touch head above level of ears	*Can you get one hand to your head without bending your neck*	Able to bring one hand to head. Head and trunk remain stable	Can only bring hand to head by flexing head	Unable to bring hand to head even using head and trunk movement			R / L
4 Two hands to head in sitting Hands touch head above level of ear	*Can you lift both hands up at the same time, to your head, without bending your neck?*	Able to place both hands on head arms free from side. Head and trunk remain stable	Able to place hands on head but only using head flexion or side tilt or crawling hands up or one at a time	Unable to place both hands on head			
5 Supine to side-lying	*Can you roll onto your side in both directions? Try not to use your hands*	Able to ½ roll from supine both ways	Can ½ roll only one way R / L	Unable to half roll either way			Shoulders perpendicular to floor. Trunk and hips in line with body
6 Rolls prone to supine over R	*Can you roll from your tummy to your back in both directions?*	Turns to supine with free arms to the right	Turns to supine using arms to push/ pull with	Unable to turn into supine			
7 Rolls prone to supine over L		Turns into supine with free arms to the left	Turns to supine using arms to push/ pull with	Unable to turn into supine			
8 Rolls supine to prone over R	*Can you roll from your back to your front in both directions?*	Turns to prone with free arms to the right	Turns to prone by pulling/ pushing on arms	Unable to turn into prone			
9 Rolls supine to prone over L		Turns to prone with free arms to the left	Turns to prone by pulling/ pushing on arms	Unable to turn into prone			
10 Sitting to lying	*Can you lie down in a controlled way from sitting?*	Able to lie down in a controlled fashion through side lying or using clothes	Able to lie down by flopping forwards and rolling sideways	Unable or falls over			
11 Props on forearms	*Can you prop yourself on your forearms and hold for a count of 3?*	Able to achieve prop on elbows with head up for a count of 3	Holds position when placed for a count of 3	Unable			
12 Lifts head from prone	*Can you lift you head up keeping your arms by your side for a count of 3?*	Able to lift head up in prone arms by side for a count of 3	Lift head with arms in a forward position for a count of 3	Unable			
13 Prop on extended arms	*Can you prop yourself up with straight arms for a count of 3?*	Able to prop on extended arms, head up for a count of 3	Can prop on extended arms if placed for a count of 3	Unable			
14 Lying to sitting	*Can you get from lying to sitting without rolling to your tummy?*	Able by using side lying	Turns into prone or towards floor	Unable			
15 Four-point kneeling	*Can you get onto your hands and knees with your head up and hold for a count of 3?*	Achieves four-point kneeling – head up for a count of 3	Holds position when placed for a count of 3	Unable			

Test	*Instruction*	2	1	0	L B C	S =	Comments S = score
16 Crawling	*Can you crawl forwards?*	Able to crawl forwards – moves all four points twice or more	Moves all four points only once	Unable			
17 Lifts head from supine	*Can you lift your head to look at your toes keeping your arms folded for a count of 3*	In supine, head must be lifted in mid-line. Chin moves towards chest. Held for a count of 3	Head is lifted but through side flexion or with no neck flexion Held for a count of 3	Unable			
18 Supported standing	*Can you stand using one hand for support for a count of 3?*	Can stand using one hand support for a count of 3	Able to stand with minimal trunk support (not hip) for a count of 3	Can stand with hand support but needs knee/hip support in addition for a count of 3 Or unable			
19 Stand unsupported	*Can you stand without holding onto anything for a count of 3?*	Can stand independently for the more than a count of 3	Stands independently for a count of 3	Stands only momentarily (less than a count of 3) Or unable			
20 Stepping	*Can you walk without using any help or aids? Show me*	Able to take more than 4 steps unaided	Able to take 2 – 4 steps unaided	Unable			
SCORE		No of 2's =	No of 1's =	No of 0's =	TOTAL =		/40
Comments							

PNCR	Expanded Hammersmith Functional Motor Scale for SMA (HFMSE) *add-on module*						07/03/09
Test	*Instruction*	2	1	0	L B C	S =	Comments S = score
21 Right hip flexion in supine	*Can you bring your right knee to your chest?*	Full hip flexion achieved	Initiates right hip and knee flexion (more than 10% of available range of motion)	Unable			
22 Left hip flexion in supine	*Can you bring your left knee to your chest?*	Full hip flexion achieved	Initiates left hip and knee flexion (more than 10% of available range of motion)	Unable			
23 High kneeling to right half kneel	*Can you bring your **left** leg up so that your foot is flat on the ground without using your arms and hold for a count of 10?*	Arms used for transition, maintains arms free in half kneel for a count of 10	Maintains half kneel with arm support for a count of 10	Unable			
24 High kneeling to left half kneel	*Can you bring your **right** leg up so that your foot is flat on the ground without using your arms and hold for a count of 10?*	Arms used for transition, maintains arms free in half kneel for a count of 10	Maintains half kneel with arm support for a count of 10	Unable			
25 High kneeling to stand leading with left leg	*Can you stand up from this position starting with your left leg without using your hands? May need demonstration*	Able with arms free	Able to shift weight off both knees (with or without arm support)	Unable			
26 High keeling to stand leading with right leg	*Can you stand up from this position starting with your right leg without using your hands? May need demonstration*	Able with arms free	Able to shift weight off both knees (with or without arm support)	Unable			
27Stand to sit	*Can you sit on the floor, in a controlled way? Try not to use your arms.*	Able to sit down with arms free and no collapse	Sits on floor but uses arms or crashes	Unable			
28Squat	*Can you squat? Pretend you are going to sit in a very low seat.*	Squats with arms free (at least 90° of hip and knee flexion)	Initiates squat (more than 10%) , uses arm support	Unable to initiate			
29 Jump 12" forward	*Can you jump as far as you can, with both feet, from this line all of the way to the other line?*	Jumps at least 12", both feet simultaneously	Jumps between 2-11", both feet simultaneously	Unable to initiate jump with both feet simultaneously			
30 Ascends stairs with rail	*Can you walk up the steps? You can use one railing*	Ascends 4 stairs with railing, alternating feet	Ascends 2-4 stairs, one rail, any pattern	Unable to ascend 2 stairs one rail			
31 Descends stairs with rail	*Can you walk down the steps? You can use one railing*	Descends four stairs , with railing, alternating feet	Descends 2-4 stairs, one rail, any pattern	Unable to descend 2 stairs with one rail			
32 Ascends stairs without rail	*Can you walk up the steps? This time try not to use the railing*	Ascends four stairs, arms free, alternating feet	Ascends 2-4 stairs, arms free, any pattern	Unable to ascend 2 stairs arms free			
33 Descends stairs without rail	*Can you walk down the steps? This time try not to use the railing*	Descends four stairs, arms free, alternating feet	Descends 2-4 stairs, arms free, any pattern	Unable to descend 2 stairs arms free			
SCORE		No of 2's =	No of 1's =	No of 0's =			TOTAL = /66

APPENDIX 2: Protocol Version 2.0

PURPOSE: The purpose of this version is as follows:

To add an additional site, update medical monitor information, and update product information, based upon FDA approval.

Risk: these administrative changes provide clarity, 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 Clinical Study Protocol,

IND Number was updated ~~106263~~ **<u>142044</u>**

Version and Date of Protocol, added text to indicate this is protocol Version 2.0

Version 2.0 dated 12 April 2019

Footer was updated to reflect new version information

Section 1 Procedures in Case of an Emergency, under Medical Monitor, changed the Name and Contact Information number.

~~**Gary Ingenito, Chief Medical Officer**~~

~~**ext. 123 gingenito@catalystpharma.com**~~

<u>Stanley Iyadurai, Vice President, Clinical Affairs</u>

<u>ext. 139 siyadurai@catalystpharma.com</u>

Section 1 Procedures in Case of an Emergency, Investigators Name and Contact Information were removed.

Section 1 Procedures in Case of an Emergency, under Contract Research Organization, information was added

For Italy, email l.cottini@highresearch.it was added.

Section 1 Procedures in Case of an Emergency, CRO information was added
Easthorn Clinical Services for countries outside Italy
Obilicev venac 15
11000 Belgrade, Serbia
Tel: +381 11 3286 305
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Section 1 Procedures in Case of an Emergency, Safety Reporting, changed address for PhAST Consulting Srl

~~**Via A. Gramsci 10**~~
~~**20090 Monza, Italy**~~

Via Roma 74 - 20060
Cassina de' Pecchi (MI) Italy

Section 2 Synopsis, under Study Site, deleted reference to single site, to reflect added site

~~**Single site in Italy**~~

Up to 3 sites

Section 2 Synopsis, Criteria for Inclusion and Exclusion, the following were removed:

2. ~~**Concomitant use of medicinal products with a known potential to cause QTc prolongation.**~~
3. ~~**Patients with long QT syndromes.**~~

Section 2 Synopsis, Criteria for Inclusion and Exclusion, criteria 4 was updated

to include the note **(objectively measured at screening).**

Table of Contents, two items with no corresponding sections were removed:

~~**2. Male or Female between the ages of 6 and 50 years**~~

~~**3. Genetically confirmed diagnosis of SMA Type 3**~~

Reference to ***Table 3 Medications Prohibited During Study***, was added to the Table of Contents. Table references throughout the document have been corrected accordingly.

Appendix 2, Quality of Life Assessments was removed, and **Appendix 2. Protocol Version 2.0** history has been added to Table of Contents.

Section 7.2 Amiphampridine, United States of America was added as a market, and Firdapse Investigator Brochure date was updated.

~~.~~ ***and the United States of America.***

~~**June 2017**~~ ***March 2019***).

The date for the Investigator Brochure (~~**June 2017**~~ **March 2019*)*** was updated in the following sections: 7, 7.2, 7.4.3, and 7.4.4.

Section 9.1.1 Overall Study Design and Plan, deleted phrase with single site reference.

The study ~~**is planned to be conducted at a single site; and**~~ will include about 12 male and female SMA Type 3 patients,

Section 9.1.1 Overall Study Design and Plan, **Error! Reference source not found.** was corrected to **Table 1**.

Table 1 Schedule of Events, was updated to include a column for **Week 3**.

Section 9.2.1 Inclusion Criteria, criteria 4 was updated to include the note **(objectively measured at screening).**

Section 9.2.2 Exclusion Criteria, the following were removed:

~~**2. Concomitant use of medicinal products with a known potential to cause QTc prolongation.**~~
~~**3. Patients with long QT syndromes.**~~

Section 9.3.2.2 Storage, the following was added:

(excursions between 15-30° may be allowed)

Section 9.4 Prior and Concomitant Medications, the following was deleted:
~~**Medications known to prolong QTc interval (e.g. fluoroquinolone antibiotics) should be used with caution, if required by the patient.**~~

Table 4 Clinical Laboratory Tests, blood chemistry item has been updated:

CO_2 **or bicarbonate**

Table 4 Clinical Laboratory Tests, under the column Urine Tests, text was changed:

~~**Hemoglobin**~~ ***Blood in urine***

Section 9.7.4 Quality of Life Assessment, the following has been added and deleted:

Each QoL evaluation is available in the local language for the appropriate sites.
~~**(Appendix 2)**~~

Section 10.6 Medical Monitor Contact Information was updated to reflect the changes made on Section 2 Synopsis.

~~**Gary Ingenito, MD, PhD**~~
~~**Chief Medical Officer**~~
~~**Catalyst Pharmaceuticals, Inc.**~~

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Section 13, Data Quality Assurance, the following sentence was deleted:

~~**A separate unblinded CRA may verify records at the site.**~~

Section 22, Signature Page, information below the Medical Monitor Signature was updated.

~~**Gary Ingenito, MD, PhD**~~
~~**Chief Medical Officer**~~

Stanley Iyadurai, MD, PhD
Vice President, Clinical Affairs

Appendix 2, Quality of Life Assessments, has been removed.

Appendix 2. Protocol Version 2.0 has been added to record changes made to this protocol.

APPENDIX 3: Protocol Version 3.0

PURPOSE: The purpose of this version is as follows:

To reconcile mismatches between Protocol SMA-001 and Protocol SMA-002.

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

MODIFICATIONS TO PROTOCOL:

On Page 1, under Clinical Study Protocol,

Version and Date of Protocol, added text to indicate this is protocol Version 3.0

Version 3.0 dated 27 September 2019

Footer was updated to reflect new version information

On Page 3 Jonathan Rubine contact details were replaced by Gary Ingenito's.

Section 2 Synopsis, Criteria for Inclusion and Exclusion, the following were added:

9. Uncontrolled asthma.
10. Concomitant use with sultopride.
11. Concomitant use with medicinal products with a narrow therapeutic window.

Section 2 Synopsis, Criteria for Inclusion and Exclusion, criteria 4 was updated

4. Treatment with an investigational drug (other than amifampridine), device, or biological agent within 6 months prior to Screening or while participating in this study.

to read as follows in order to match Protocol section 9.2.2

4. Treatment with an investigational drug (other than amifampridine), device within 6 months prior to Screening or while participating in this study.

Section 9.2.2. Exclusion Criteria, the following were added:

9. Uncontrolled asthma.
10. Concomitant use with sultopride.
11. Concomitant use with medicinal products with a narrow therapeutic window.

Section 9.4 Prior and Concomitant Medications, the following was inserted: Medications that are contraindicated when combined with amifampridine phosphate are:

- Medicinal products with narrow therapeutic window
- Sultopride

Amifampridine phosphate should be used with caution when combined with the following products:

- Medicinal products known to lower the epileptic threshold
- Medicinal products with atropinic effects
- Medicinal products with cholinergic effects
- Non depolarizing muscle relaxant acting medicinal products
- Depolarizing muscle relaxant acting medicinal products.

Table 3 updated.

Appendix 3. Protocol Version 3.0 has been added to record changes made to this protocol.