PROTOCOL SMA-001

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

STATISTICAL ANALYSIS PLAN

Version 1.0

11 May 2020

CONFIDENTIAL

Submitted to:

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1 Statistical Analysis Plan Signature Form

Statistical Analysis Plan Final Version 1.0 (Dated 11 May 2020) for SMA-001 Study.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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2 Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	11MAR2020	Claudio Iannacone	n.a.
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1.0	11MAY2020	Claudio Iannacone	Approved version.

3 List of Abbreviations and Definitions of Terms

Abbreviation	Definition
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
BMI	Body mass index
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

Abbreviation	Definition
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
PPAS	per protocol analysis set
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)
SAF	safety analysis set
SAP	statistical analysis plan
SAS	Statistical Analysis System (software)
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

Abbreviation	Definition
US	United States
WHO-DD	World Health Organization – Drug Dictionary

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4 Introduction

This Statistical Analysis Plan (SAP) is based on study procedures and analyses from the protocol, Version 1.0, dated 20 November 2017. This SAP takes as well into account the following protocol versions/amendments:

- Version 2.0, dated 12 April 2019
- Version 3.0, dated 27 September 2019

Table shells and mock listings corresponding to the contents of this document will be prepared and included with the final version. This document, with table shells and mock listings, will be reviewed prior to final unblinded analyses, and revised if necessary.

4.1 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 multisystem 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.

5 Trial Design

5.1 Study 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.

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;

5.2 Study Design

This is a stratified, randomized (1:1), double-blind, placebo-controlled, 2-treatment, 2-sequence, crossover study.

Patients will be randomized (1:1) to one of two sequences:

AP: Amifampridine (Period 1) followed by Placebo (Period 2)

PA: Placebo (Period 1) followed by Amifampridine (Period 2)

Patients will be randomized on the last day of the open-label run-in period (Day 0).

IP will be administered under double-blind conditions. Randomized patients who discontinue after initiation of treatment may be replaced. 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.

The study is planned to be conducted in two investigational sites; and will include about 12 male and female SMA Type 3 patients.

5.3 Study Drug Dosage and Administration

The 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.

A placebo equivalent will be provided as tablets indistinguishable from the amifampridine tablets and will be administered consistent with the dose regimen of amifampridine.

6 Sample Size, Randomization and Blinding

6.1 Sample Size

The sample size for this study was based on clinical considerations related to the epidemiology of the disease, and not on a formal statistical power calculation. It is anticipated approximately 12 patients will be randomized with 6 patients per treatment sequence.

6.2 Randomization and Blinding

Patients will be randomized to one of two sequences:

AP: Amifampridine (Period 1) followed by Placebo (Period 2)

PA: Placebo (Period 1) followed by Amifampridine (Period 2)

This is a double-blind study where all involved parties will be blinded to randomized assignment to the two sequences.

7 Selection and Discontinuation of Patients

7.1 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.

7.2 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.

7.3 Removal of Patients from Treatment or Assessment

Patients may withdraw their consent to participate in the study or to receive treatment at any time without prejudice. The investigator or Catalyst may withdraw a patient from the treatment or from the study at any time.

8 Schedule of Events

The schedule of clinical procedures and assessments conducted during the study is presented in Appendix 1.

9 Study Endpoints

9.1 Efficacy Endpoints

The following efficacy assessments will be performed as described in the Schedule of Events (Appendix 1), following the sequence in the following listed below.

Order of Assessment at Each Study Visit (when applicable)	Start Time After Dose (+10 minutes unless otherwise specified)
HFMSE	**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

9.1.1 Hammersmith Functional Motor Scale Expanded (HFMSE)

The HFMSE 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 HFMSE 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 HFMSE shows good test-retest reliability and correlation with other clinical measures in SMA, especially in Type 3.

9.1.2 6-minute walk test

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

9.1.3 Timed items

a) Rising from floor – the time required in rising from the supine position

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

9.1.4 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.

9.2 Safety Endpoints

Safety endpoints include treatment-emergent adverse events (AEs), vital signs, physical examination, clinical laboratory tests (hematology, chemistry and urinalysis), and ECGs, and each corresponding CFB as appropriate.

10 Data Analysis and Statistical Considerations

Statistical tables and by-patient data listings will be prepared using SAS System (SAS Institute, Cary, North Carolina, USA), Version 9.4 under Windows 10 PRO.

10.1 Analysis Populations

The following analysis populations have been defined for this clinical study:

a) **Enrolled Population (EP)**: all patients who provided informed consent for this study.
b) **Safety Population (SAF)**: the safety population consists 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.
c) **Full Analysis Set (FAS):** this population consists of all randomized subjects who receive at least one 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.
d) **Per-Protocol Population (PPAS)**: this population is a subset of the FAS population, excluding subjects with major protocol deviations. The PPAS 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 PPAS 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 PPAS population will be used for selected effectiveness analyses. The results obtained in PPAS population set will be seen as supportive of those obtained in the FAS population.

10.2 General Statistical Considerations

The following standards will be applied for the analyses unless otherwise specified.

Simple summary statistics (descriptive statistics) for continuous data will be n (number of non-missing observations), mean, median, standard deviation, minimum, and maximum.

The frequency count and percentage will be used to summarize categorical data. Summary statistics will be presented by treatment by period and overall.

Summary statistics for all safety and efficacy variables will be presented by sequence, except for tables related to incidence of AEs which will be presented by treatment group.

All tables of baseline and demographic data will be presented by sequence.

All data collected will be presented in the by-patient data listings, sorted by patient and by period and day, where appropriate.

P-values <0.05 will be considered as statistically significant.

95% confidence interval will be calculated as appropriate.

Change From Baseline (CFB) will be summarized for efficacy and safety assessments, where Baseline is defined as Day 0.

10.3 Multiple Comparisons/ Multiplicity

No alpha adjustment for multiple comparisons will be introduced, because only the comparison between amifampridine and placebo group on the primary efficacy endpoint will be considered as confirmatory.

10.4 Examination of Subgroups

No subgroup analyses are foreseen for this study.

10.5 Interim Analysis

There will be no Interim Analysis for this study.

10.6 Final Analysis

All final, planned analyses identified in this SAP will be performed by SPARC Consulting, Milan, Italy on behalf of Catalyst Pharmaceuticals following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Study Treatment.

10.7 Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries.

Listings will include scheduled, unscheduled and early discontinuation data.

10.8 Windowing Conventions

Actual dates of visits will be used for calculations of time intervals. No visit windowing will be performed for this study. Out-of-window visits will not be reallocated to the nearest timepoint.

10.9 Demographic Characteristics and Medical History

10.9.1 Demographic Characteristics

Demographic parameters, including age, gender, race, body weight, height, and BMI at Screening, will be summarized for the SAF analysis set.

10.9.2 Medical History

Summary analysis will involve the SAF analysis set.

SMA history parameters, including time in years from onset of SMA symptoms, previous treatments for SMA and SMN gene analysis results will be summarized by treatment sequence.

Time from onset of SMA symptoms will be calculated as the difference in years from the year of the date of informed consent and the year of onset of SMA symptoms reported in CRF.

All verbatim terms reported in the Medical History form will be assigned to a Preferred Term (PT) and will be classified by the primary System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, version 23.

Previous diseases are those reported in the "Medical History" form of the eCRF with item "*Present at study start*?" flagged as "No".

Concomitant diseases are those reported in the "Medical History" form of the eCRF with item "*Present at study start*?" flagged as "Yes" or "Unknown".

The following data will be presented by treatment sequence:

a) A default frequency table showing the number and percentage of patients who exhibited an abnormality by single body system;
b) A default frequency table showing the number and percentage of patients who exhibited at least one previous disease and the previous diseases by primary SOC and PT;
c) A default frequency table showing the number and percentage of patients who exhibited at least one concomitant disease and the concomitant diseases by primary SOC and PT;

Medical history will be listed for all enrolled patients.

10.10 Medication and Treatment Analysis

10.10.1 Patient Disposition and Accountability

The number and percentage of randomized patients who are in the SAF, FAS, and PPAS analysis set, and who complete each treatment period will be presented by treatment sequence. The number and percentage of patients who discontinue dosing prematurely, along with the primary reason that dosing was discontinued prematurely, will be presented by period and treatment at the time of discontinuation.

10.10.2 Duration of Treatment and Compliance

Duration of treatment during the open-label period will be summarized for the Safety Population. The duration of treatment during the open-label run-in period is the date of Day 0 minus date of first study dose+1.

Duration of treatment during the double-blind periods will be summarized for the Safety Population by treatment and by period and pooled.

For Period 1, the duration of treatment is the (date of Day 14 minus date of Day 0)+1; for patients who discontinue during Period 1, the duration of treatment during Period 1 is the (date of the last dose during Period 1 minus the date of Day 0) +1.

For Period 2, the duration of treatment is the (date of Day 28 minus date of Day 14)+1; for patients who discontinue during Period 2, the duration of treatment during Period 2 is the (date of the last dose during Period 2 minus the date of Day 14)+1.

The overall duration during the double-blind periods will be obtained for each treatment by adding the durations for the periods during which the patient received each treatment.

Compliance is 100%*(Number consumed)/(Number prescribed). "Number consumed" is from Study Drug Accountability and "Number prescribed" is number of tablets to have been taken daily duration.

Compliance during the double-blind periods will be summarized for the Safety Population by treatment and by period. The compliance during the double-blind periods will be obtained for each treatment by performing the same calculations for the periods during which the patient received each treatment.

10.10.3Concomitant 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.

Concomitant medications will be only listed for all enrolled patients.

10.11 Efficacy Analyses

The primary assessment of efficacy will be performed using the CFB in HFMSE total score.

Secondary assessments of efficacy will be performed using the following endpoints:

1. CFB in 6-minute walk test (meters);
2. CFB in rising from floor (seconds);
3. CFB in rising from a chair (seconds);
4. CFB in climbing 4 steps (seconds);
5. CFB in walking 10 meters (seconds);
6. CFB in the INQoL subscales scores:

   Symptoms (section 1):

   a) Weakness
   b) Muscle “locking”
   c) Pain
   d) Fatigue
   e) Droopy eyelids
   f) Double vision
   g) Swallowing difficulties

   Life domains (section 2):

   a) Activities
   b) Independence
   c) Social relationship
   d) Emotions
   e) Body image

   Life domains (section 3):

   a) Perceived treatment effects
   b) Expected treatment effects

Quality of Life

7. CFB in the PEDSQL score (where applicable).

The individual domain scores in INQoL and PedsQL will be calculated using the scoring algorithms outlined in Appendix 2.

The efficacy assessments will be summarized by sequence and period.

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. The 95% confidence interval (CI) based on this model will be presented for the difference in the Least Squares (LS) means. The analysis will be performed using SAS PROC MIXED to incorporate the random effects model.

A summary statistics on the CFB in the individual items score of the HFMSE will be also provided by sequence and period.

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 HFMSE 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. The 95% confidence interval (CI) based on this model will be presented for the difference in the Least Squares (LS) means. The analyses will be performed using SAS PROC MIXED to incorporate the random effects model.

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

Analysis of the primary efficacy endpoint will be perfomed both in the FAS and in PPAS analysis set. Analysis on FAS analysis set will be considered as primary while analysis in the PPAS will be used as supportive of the FAS results.

Analysis of secondary efficacy endpoints will be performed only in the FAS analysis set.

10.12 Safety Data

Summaries of safety data will be presented for the SAF analysis set using observed data only, i.e. without imputation. All observed safety data will be listed.

10.12.1 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 Protocol Section 10.2.

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

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

The Investigator will determine the severity of each AE using grades defined in Table 1 (the event will be recorded on the source documents and AE CRF). Events that are Grades 4 and 5 are serious events and require completion of both an SAE form and AE CRF.

Table 1 - Categories of Severity 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.

A treatment-emergent adverse event (TEAE) is any AE that emerges after randomization having been previously absent, or worsens relative to the previous periods. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0. All treatment-emergent adverse events (TEAEs) will be summarized by the treatment at the time of onset. Counts and percentages will be presented by treatment for each observed system organ class (SOC) and preferred term (PT) as defined in MedDRA. A patient having more than one TEAE with the same PT in a given time period will be counted only once in the incidence calculation for that PT for that time period. Similarly, if a patient has more than one TEAE in the same SOC in a given time period, the patient will be counted only once in the total number of patients with a TEAE for that SOC for that time period. TEAEs will summarized only for the treatment at onset unless it worsens at subsequent period(s) or recurs after having resolved at a previous period; in each of these situations, the TEAE will be considered a new TEAE and summarized for both treatments.

Each TEAE will be assessed with respect to severity and relationship to treatment. The relationship of an AE will be recorded using the specified relationship categories described in Table 2.

Table 2 - Description of relationship to adverse events 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.

The following summary tables will be provided:

1. An overview of TEAEs including the number of TEAEs, related TEAEs, TESAEs, related TESAEs, TEAEs leading to premature discontinuation, TEAEs leading to hospitalization, life-threatening TEAEs, number of patients with at least one TEAE, at least one related TEAE, at least one TESAE, at least one related TESAE, at least one TEAE leading to premature discontinuation, at least one TEAE leading to hospitalization, at least one life-threatening TEAE, and at least one TEAE leading to death

2. Summary of all TEAEs by treatment group, Primary SOC and PT
3. Summary of all related TEAEs by treatment group, Primary SOC and PT
4. Summary of all TESAEs by treatment group, Primary SOC and PT
5. Summary of all related TESAEs by treatment group, Primary SOC and PT
6. Summary of all TEAEs leading to hospitalization by treatment group, Primary SOC and PT
7. Summary of all life-threatening TEAEs by treatment group, Primary SOC and PT
8. Summary of all TEAEs leading to premature discontinuation by treatment group, Primary SOC and PT
9. Summary of all TEAEs by treatment group, Primary SOC and PT and maximum severity

The following individual data listings will be produced:

1. A listing of all TEAEs
2. A listing of all TESAEs
3. A listing of all IMP related TEAEs
4. A listing of all IMP related TESAEs
5. A listing of all TEAEs leading to hospitalization
6. A listing of all life-threatening TEAEs
7. A listing of TEAEs leading to premature discontinuation
8. A listing of all TEAEs leading to death
9. A listing of all AEs started before the first dose of study drug intake
10. A listing of all AEs started after the first dose of study drug intake but before the date of randomization (Day 0)

10.12.2 Vital Signs and Body Weight

Vital signs, including sitting blood pressure (systolic and diastolic; mmHg), sitting heart rate (beats/minute), body temperature (^{o}C), respiration rate (breaths/minute), and weight (kg) will be summarized using descriptive statistics by sequence and period for both the observed values and CFB.

Height will be recorded at Screening visit only.

BMI will be calculated at Screening visit according to the following formula:

BMI (kg/m^2) = ((body weight (kg)/(height (m))^2).

Height and BMI will be summarized using descriptive statistics by sequence.

10.12.3 12-Lead ECG

Analysis will be performed in the SAF analysis set.

A standard 12-lead ECG will be recorded at Screening, Days 0 and Day 28 visit.

Each tracing will be classified as “Normal tracing”, “Abnormal tracing (not clinically significant)”, “Abnormal tracing (clinically significant)”, or “Unknown”.

A summary of the assessments will be provided by sequence and period. Clinically significant changes from baseline will be recorded as AEs.

ECG abnormalities reported will be coded using MedDRA thesaurus version 23.0, and the terms listed for all enrolled patients.

10.12.4 Physical Examination

Summary analysis will involve the SAF analysis set.

A complete physical examination is to be performed at Screening, Days 0, and Day 28.

These assessments will be summarized by sequence and period using counts and percentages.

All verbatim terms reported in the Physical Examination form will be assigned to a Preferred Term (PT) and will be classified by the primary System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, version 23.

A summary table containing the frequency and percentage of patients who exhibited at least one abnormality as well as of the abnormalities reported at Screening, Day 0 and Day 28 by primary SOC and PT will be prepared by treatment sequence.

Physical examination abnormalities will be listed for all patients.

10.12.5 Laboratory Tests

For blood chemistry and hematology, descriptive statistics will be presented for the observed value and CFB by sequence and visit. The frequency and percentage of patients who experience abnormal (i.e. outside of reference ranges) laboratory values and clinically significant abnormalities will be presented by sequence and visit.

Moreover shift tables from screening to each time-point, with regard to the laboratory normal range (low, normal and high), will be presented for all parameters of blood chemistry and hematology by sequence. The laboratory parameters to be collected are given below in Table 3.

Table 3 - Clinical Laboratory Tests

Blood Chemistry	Haematology	Urine Tests
Albumin	Haemoglobin	Appearance
Alkaline phosphatase	Haematocrit	Color
ALT (SGPT)	WBC count	pH
AST (SGOT)	RBC count	Specific gravity
Direct bilirubin	Platelet count	Ketones
Total bilirubin	Differential cell count	Protein
BUN		Glucose
Calcium		Bilirubin
Chloride		Nitrite
Total cholesterol		Urobilinogen
CO_2		Hemoglobin
Creatine phosphokinase		
Creatinine		
Glucose		
GGT		
LDH		
Phosphorus		
Potassium		
Total protein		
Sodium		
Uric acid		

Urinalysis parameters will not be included in summary tables.

All laboratory parameters will be listed for all patients.

10.12.5.1 Laboratory Specific Derivations

For each laboratory parameter, where appropriate, the reported values will be converted into SI units and if needed boundary values for reference ranges will be converted as well.

Conversion to SI will be provided using textbook ranges: *SI Unit Conversion Guide, M. Laposata, NEJM, 1992*.

To convert from the conventional unit to the SI unit, multiply by the conversion factor:

Table 4 - Clinical Laboratory Tests SI Conversion Factors

Component	Conventional Unit	Conversion Factor	SI Unit
Hematology			
RBC count	x 10^6/µL	1	x 10^{12}/L
WBC count	x 10^3/µL	1	x 10^9/L
Neutrophils	x 10^3/µL	1	x 10^9/L
Lymphocytes	x 10^3/µL	1	x 10^9/L
Monocytes	x 10^3/µL	1	x 10^9/L
Eosinophils	x 10^3/µL	1	x 10^9/L
Basophils	x 10^3/µL	1	x 10^9/L
Platelet count	x 10^3/µL	1	x 10^9/L
Hemoglobin	g/dL	10	g/L
Hematocrit	%	0.01	Proportion of 1.0
Biochemistry			
Albumin	g/dL	10	g/L
Alkaline phosphatase (ALP)	U/L	1	U/L
ALT (SGPT)	U/L	1	U/L
AST (SGOT)	U/L	1	U/L
Direct Bilirubin	mg/dL	17.104	µmol/L
Total Bilirubin	mg/dL	17.104	µmol/L
BUN	mg/dL	0.357	mmol/L
Calcium	mg/dL	0.25	mmol/L
Chloride	mEq/L	1.0	mmol/L
Total cholesterol	mg/dL	0.02586	mmol/L
CO_2	mEq/L	1	mmol/L
Creatinine phosphokinase	U/L	0.01667	µkat/L
Creatinine	mg/dL	88.4	µmol/L
Glucose	mg/dL	0.05551	mmol/L

Component	Conventional Unit	Conversion Factor	SI Unit
Gamma-GT	U/L	1	U/L
LDH	U/L	0.01667	µkat/L
Phosphorus	mg/dL	0.3229	mmol/L
	mEq/L	1.0	mmol/L
Potassium	mg/dL	0.2558	
Total protein	g/dL	10	g/L
Sodium	mEq/L	1.0	mmol/L
Uric acid	mg/dL	59.48	µmol/L

10.13 Protocol Deviations

All the protocol deviations will be discussed case by case by the clinical team during the review of the data before the lock of the study database and described in the Blind Data Review Report.

However, the following protocol deviations are anticipated to be considered as major:

- Inclusion and exclusion criteria not respected;
- Received treatment other than they were randomized to;
- Missing information on IMP administration that does not allow calculation of IMP exposure/compliance;
- Overall study treatment compliance < 80%;
- Missing data for the primary endpoint (CFB in HFMSE total score);
- Use of prohibited medications during study (see Protocol Section 9.4).

The number and percentage of patients with each type of protocol deviation will be presented by treatment.

11 Data Handling

11.1 Multicenter Sites

This study is conducted by multiple Investigators in two investigational sites.

Site-related differences will not be evaluated and presented in the statistical output as the study does not foresee a randomization stratified by Centre.

11.2 Handling of Missing Data

If a patient discontinues during a double-blind treatment period and assessments are made upon discontinuation, then these values will be used as the assessments for that period. Otherwise, missing data due to discontinuation will not be imputed. Missing safety data will not be imputed.

Handling of missing data in INQoL is provided in the Appendix 2.

12 Changes from the Protocol

No changes from the statistical analyses planned in the study protocol have been introduced in this SAP.

13 Table Shells and Specifications

13.1 Table Specifications

Tables will be provided as defined by the table shells.

Similar tables based on different populations will have the same number, except for the last digit.

All output will be generated by SAS and exported into a Microsoft Word document in RTF format. All output will be in landscape orientation. Left and right margins will be 2 cm from the side; the top and bottom margins will be 2.5 cm. Font size will be Courier New 7 pt.

The header containing the sponsor name (Catalyst Pharmaceuticals) and protocol number will appear on the top left corner of each page of the output. The page number, in the format of "Page x of y", will appear on the top right corner of the output, where y = last page of corresponding output.

Column headers in tables include the total possible numbers to be included in summaries for that table, designated as "(N=XX)".

The SAS program name, the date of the creation of the output (run date) and the reference to the data listing(s) from which the table is derived will appear on the bottom left corner as follows:

Source: [program name].sas, Run on ddmmmyyyy

Source: Listing(s) xx.x.x, xx.x.x

13.1.1 Table Format Specification

Maximum and minimum values will be reported with the same number of decimal places as collected. Means and medians will be reported to one additional decimal place. Standard deviations and standard errors will be reported to two decimal places more than the collected data. Percentages will be reported with one decimal place.

Data in the tables are formatted as follows:

Text fields in the body of the tables and listings will be left-justified.

When no data are available for a table, an empty page with the title will be produced with suitable text. Example: THERE WERE NO SERIOUS ADVERSE EVENTS.

13.2 Line Listings Specifications

Individual line listings will be provided as defined by the listing shells.

All output will be generated by SAS and exported into a Microsoft Word document in RTF format. All output will be in landscape orientation. Left and right margins will be 2 cm from the side; the top and bottom margins will be 2.5 cm. Font size will be Courier New 7 pt.

The header containing the sponsor name (Catalyst Pharmaceuticals) and protocol number will appear on the top left corner of each page of the output. The page number, in the format of "Page x of y", will appear on the top right corner of the output, where y = last page of corresponding output.

The SAS program name and the date of the creation of the output (run date) will appear on the bottom left corner as follows:

Source: [program name].sas, Run on ddmmmyyyy.

14 Programming Conventions for Outputs

Outputs will be presented according to the standard SPARC's layout of tables and line listings.

Dates & Times: depending on data available, dates and times will take the form ddmmmyyyy hh:mm (i.e. 01JAN2019 10:20)

Spelling Format: English US.

Listings: all listings will be ordered by the following (unless otherwise indicated in the template):

- Site ID
- Randomization number
- Sequence (where applicable)
- Study visit
- Study treatment
- Date and hours (where applicable)
- For listings where non-randomized patients are included, these will appear in a category after the randomized treatment groups labelled ‘Not Randomized’.

In all listings missing data will be reported, according to the variable type, as follows:

- Character variables and dates will be presented as empty fields
- Numerical variables will be presented with a “-“

Appendix 1: Schedule of Events

Study Assessment or Event [b]	Screening	Run-in		Period 1		Period 2	
	Days -14 to -1	Start [a] Day 1	Last Visit 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
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
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
Concomitant medications	X	X	X	X	X	X	X
Patient Dosing Diary Provided		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.

[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.

[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.

Appendix 2: INQoL and PedsQL Scaling and Scoring

Scaling and scoring INQoL_English.pdf

Scaling and scoring of PedsQL English.pdf