Cover Page for Protocol

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Official title of study	Long Term Safety Study of Amifampridine Phosphate in Patients with MuSK Antibody Positive and AChR Antibody Positive Myasthenia Gravis Patients
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STATISTICAL ANALYSIS PLAN

Final v2.0

Protocol: MSK-003 (Amendment to the Final Version 1, 07 February 2020)

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

Date: February 21, 2023

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LIST OF ABBREVIATIONS

AE	***Adverse Events***
AChR-MG	***Acetylcholine receptor Myasthenia Gravis***
CRF	***Case Report Form***
DBP	***Diastolic Blood Pressure***
DSUR	***Development Safety Update Report***
ECG	***Electrocardiograms***
FDA	***Food and Drug Administration***
ICF	***Informed Consent Form***
ICH	***International Committee for Harmonization***
MedDRA	***Medical Dictionary for Drug Regulatory Affairs***
MG-ADL	***Myasthenia Gravis Activities of Daily Living***
MuSK-MG	***Muscle-specific receptor tyrosine Kinase-Myasthenia Gravis***
PBRS	***Peachtree BioResearch Solution***
PT	***Preferred Term***
SAE	***Serious Adverse Events***
SAP	***Statistical Analysis Plan***
SAS	***Statistical Analysis System***
SBP	***Systolic Blood Pressure***
SOC	***System Organ Class***
TEAE	***Treatment-Emergent Adverse Events***
US	***United States***
WHODRUG	***World Health Organization Drug Dictionary***

1. INTRODUCTION

1.1 Objectives

The present long-term extension study will evaluate safety and tolerability of amifampridine on clinical laboratory test variables, ECGs, AEs, vital signs, physical examinations and the effects on MG-ADL score over several months in patients with MuSK-MG or AChR-MG. is needed to demonstrate that the product is safe and in patients with MG.

- The primary objective of the study is to evaluate the long-term safety and tolerability of amifampridine in patients with MuSK-MG; and with AChR-MG.
- The secondary objective of the study is to assess the effect of amifampridine phosphate on Myasthenia Gravis Activities of Daily Living Score (MG-ADL).

This Statistical Analysis Plan (SAP) corresponds to the Statistical Approach section of Clinical Protocol MSK-003, amendment, dated February 07, 2020, with additional changes included to the Version 1.0 dated 25 Oct 2022.

1.2 Design

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

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

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

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

The only efficacy measurement is the MG-ADL which will be completed every 3 or 6 months. Safety and tolerability assessments will be made every 3 or 6 months or more frequently at the discretion of the Investigator. The study will continue until amifampridine is approved by Regulatory Agencies or until development of the product for this indication is halted or until month 39 is reached. The Investigator may alter the dose and dosing frequency during the Long-Term Study as well as schedule additional clinic visits for any reason.

Patients will be seen in the clinic at the end of Months 3, 6, 9, 12, 15, 21, 27, 33 and 39. In between the 3-or 6-month visits, patients may also have telephone/video contact with the site, or unscheduled visits, if needed.

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

2. ELABORATION OF STUDY PROTOCOL

2.1 Study Populations

- Safety Population: All enrolled patients who receive at least one dose of study drug will be included in the safety population.

All analyses will be performed on the safety population.

2.2 Study Endpoints

2.2.1 *Safety Endpoint*

Safety endpoints of this study are:

- Incidence of patients experiencing treatment-emergent adverse events (TEAEs)
- Incidence of patients experiencing study drug-related TEAEs
- Incidence of patients experiencing equal or greater than Grade 3 TEAEs Incidence of patients discontinuing from the study due to TEAEs
- Physical exam and weight
- Vital signs including systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate, respiration, and body temperature
- Clinical laboratory tests, including hematology, chemistry and urinalysis
- Concomitant medication review
- Electrocardiogram (ECG) parameters

2.2.2 *Efficacy Endpoint*

Efficacy endpoint of this study is change in MG-ADL score over time.

2.3 Sample Size

The study is not powered with respect to any endpoint, but is an observational study to assess long term safety and lack of tolerance to the effects of amifampridine on MG-ADL. No sample size power calculation was conducted for this study.

3. STATISTICAL METHODS

3.1 General

All data will be analyzed using the Statistical Analysis System (SAS®; Version 9.2 or higher).

Continuous variables will be presented by descriptive statistics: n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be tabulated by frequency count and percentage. No hypothesis testing will be performed.

3.1.1 *Display of Decimal Places*

Means and medians will be reported to one decimal place more than the original unit reported on the case report form (CRF) or by the laboratory/vendor. Standard deviations will be reported to two decimal places more than the original unit. Minimum and maximum values will be reported to the same number of decimal places displayed on the CRF or by the laboratory/vendor.

3.1.2 *Visit Windowing*

For Vital signs, ECG, Lab and physical exam, the following protocol-specified visits are further defined for summary tables as below.

- Screening Visit (Baseline): the day subject was screened following the ICF signing
- Follow-up visit (3 Months): the visit date was most close to 91 days after baseline visit.
- Follow-up visit (6 Months): the visit date was most close to 183 days after baseline visit.
- Follow-up visit (9 Months): the visit date was most close to 274 days after baseline visit.
- Follow-up visit (12 Months): the visit date was most close to 365 days after baseline visit.
- Follow-up visit (15 Months): the visit date was most close to 456 days after baseline visit.
- Follow-up visit (21 Months): the visit date was most close to 640 days after baseline visit.
- Follow-up visit (27 Months): the visit date was most close to 822 days after baseline visit
- Follow-up visit (33 Months): the visit date was most close to 1005 days after baseline visit
- Follow-up visit (39 Months): the visit date was most close to 1187 days after baseline visit

For completed subjects, Follow-up visit (39 Months) is considered End of study visit.
For discontinued subjects, if the assessments at the scheduled visit prior to the early termination (ET) visit were not done, the ET visit will be assigned as the prior scheduled visit. Otherwise, the ET visit will be assigned to the next scheduled visit.

Other visits will be listed as “Unscheduled Visits”, and data collected at unscheduled visits will not be included in the summary table, but will be presented in the data listings.

3.1.3 *Missing Data Handling*

In general, all categories that appear on the CRF and in summary table templates will be reported even if no patients reported that category (e.g., if there are no patients of a particular race). The “Missing” category displayed for categorical variables in summary table templates will only be displayed if missing observations are present. If no observations meet the criteria for inclusion in a data display (e.g., if there are no SAEs), the table or listing will be generated with a line in the body of the listing such as “None reported.”

No imputation will be conducted for the missing data.

3.1.4 *Sub-group Analyses*

All safety endpoints will be analyzed by MG type: MuSK-MG and AChR-MG.

3.2 Subject Disposition, Demographics, Baseline Characters and Study Drug Compliance

3.2.1 *Patient Disposition*

Study completion status will be summarized for all patients. The duration of treatment will be summarized for treated patients. Categories summarized will include patients who were planned, screened, screen failure, enrolled, received study drug, completed the study, were lost to follow-up, or withdrew early. Reasons for screen failure and withdrawal will be summarized.

3.2.2 *Protocol Deviations*

Individual protocol deviations will be presented in a data listing.

3.2.3 *Demographics and Baseline Characters*

Demographic characteristics of all patients enrolled will be summarized descriptively. The summary will include age, gender, race/ethnicity, height, weight.

3.2.4 *Study Drug Exposure*

The treatment duration (day), the total dose (mg) of study drug administered, average daily dose of study drug, and study drug compliance (%) will be tabulated.

- Treatment Duration (day) is calculated as The Last Dose Date – The First Dose Date +1. If the last dose date is missing, then the last visit date will be used.
- Total Dose (mg) will be calculated as the sum of the daily dose (mg) over the Treatment Duration, considering different doses during individual time periods within the study, as documented in the IP Accountability eCRF page.
- Average Daily Dose (mg) will be calculated as Total Dose (mg) / Treatment Duration (day). This will be calculated considering each time period and Daily dose during that period, as documented in the IP Accountability eCRF page.
- Study Drug Compliance (%): 100 × Total Dose Taken (mg) / Total Dose Prescribed (mg)

3.3 **Safety Analysis**

3.3.1 *General*

All safety summaries will be presented overall for the safety population. The evaluation will take into account the recorded adverse events (AE), clinical laboratory tests, vital signs, physical exam, ECG assessments and concomitant medications.

3.3.2 *Adverse Events*

Since patients started taking study medication before enrolled the study, all AE reported are considered as treatment-emergent adverse events (TEAE).

Tabular summaries will be provided by indication for the number and percentage of patients with:

- Any TEAE by SOC and PT. This summary will include the number of unique events reported.
- Any study drug-related TEAE by SOC and PT
- Any TEAEs by SOC, PT and maximum severity
- Any treatment-emergent serious adverse event (TESAE) by SOC and PT
- Any TEAE that results in patient discontinuation from the study by SOC and Preferred Term (PT)

A listing of all adverse events will be provided. In addition, separate data listings will be presented for the following:

- Patient deaths

- Serious Adverse Events (SAEs)
- Listing of Grade 3 (Severe) or Grade 4 (Life-threatening) AEs
- Listing of AEs leading to study discontinuation

3.3.3 *Vital Signs*

A summary of values and changes from Baseline will be provided by vital signs parameter and visit of at 3, 6, 9, 12, 15, 21, 27, 33 and 39 months.

3.3.4 *Electrocardiogram (ECG)*

Each over-read ECG interval and change from baseline in each interval will be summarized descriptively by visit at 3, 6, 9, 12, 15, 21, 27, 33 and 39 months

Treatment-emergent cardiac abnormalities, as well as the overall interpretation, will be summarized. Treatment-emergent ECG findings considered by the investigator to be clinically significant will be presented only in a listing.

3.3.5 *Clinical Laboratory Assessments*

A summary of laboratory values and changes from Baseline will be provided by test and visit of at 3, 6, 9, 12, 15, 21, 27, 33 and 39 months. In addition, laboratory measures out of range or abnormal will be presented for each visit. Values deemed clinically significant by the Investigator will not be summarized, but will be presented in a listing.

3.3.6 *Physical Examinations*

The number and percent of patients with physical examination abnormalities will summarized by body system and visit of at 3, 6, 9, 12, 15, 21, 27, 33 and 39 months.

3.3.7 *Concomitant Medications*

A detailed listing of any concomitant medication taken by a patient during the course of the study will be provided. All medications, including those taken prior to study drug administration, will be listed by indication and sorted by patient and medication start date.

The following summaries will be provided by drug class and WHODRUG preferred term:

- Prior medications (medications started prior to taking study medication),
- Concomitant medications (medications started during study treatment),
- Ongoing medication (medications given during treatment, and still ongoing after completed study).

3.4 **Analysis Report**

Multiple interim analyses may be conducted upon requested. For example, the annual development safety update report (DSUR) and/or 120 Day safety update. The final study report will be conducted after study completed. One database lock is planned for this study at the end of the study.

3.5 **Key Data Items**

Study Analysis Population Definition:

- All Subjects: All subjects, including screening failures, who provided clinical information in the database.
- Safety Population: All enrolled subjects who receive at least one dose of study drug.

Important Derived Variables:

- Age (in year) = (Screening Date – Date of Birth +1)/365.25.
- Prior Medications and Treatments: The medications and treatments started before enrolled to the study (date of Informed Consent signed)
- Concomitant Medication and Treatments: The medications and treatments started on or after the date of Informed Consent signed
- Baseline: All safety measurements collected at Day 1 or before the first dose of study drug will be used as baseline
- Post Baseline Visit: follow up visit of 6, 9, 12, 15, 21, 27, 33 and 39 months after baseline and etc, or unscheduled visit after first dose of the study drug
- Study Day for follow-up visit: The visit date – Baseline date +1
    - Follow-up visit at 3 months: The visit that is closest to study day 91
    - Follow-up visit at 6 months: The visit that is closest to study day 183
    - Follow-up visit at 12 months: The visit that is closest to study day 365
    - Follow-up visit at 15 months: The visit that is closest to study day 456
    - Follow-up visit at 21 months: The visit that is closest to study day 640
    - Follow-up visit at 27 months: The visit that is closest to study day 822
    - Follow-up visit at 33 months: The visit that is closest to study day 1005
    - Follow-up visit at 39 months: The visit that is closest to study day 1187
- Duration of Disease (year):

  (Date of Informed Consent signed – Date of original Diagnosis +1) / 365.25
- Study drug compliance (%): 100 × Total Dose (mg) / Total Prescribed Dose (mg), where total dose taken will be calculated as (Dispensed # - Retuned # - Lost #) × 10 mg (refer to CRF IP Accountability page (DA domain), and the total prescribed dose is collected at each IP accountability CRF (EX domain)
- Treatment emergent Adverse Events (TEAE): All AEs reported in this study are TEAE

Formulas of Metric Conversion:

- 1 inch = 2.54 cm
- 1 lb = 0.4536 kg
- $^{o}C = (^{o}F – 32)x5/9$

3.6 Change to Planned Protocol Analysis

In a randomized, placebo-controlled MSK-002 study, amifampridine phosphate was not effective in demonstrating a difference over placebo in MG-ADL score change from Day 0 (Baseline) to Day 10. Based on the sponsor decision, no statistical analysis will be conducted for the efficacy endpoint, change from baseline in MG-ADL score.

4. OUTPUT PLANNED FOR THE STUDY REPORTS

4.1 Tables Planned for Interim Reports and Final Study Report

Table #	Table Title	CSR	DSUR
T01	Subject Disposition (All subjects)	X	X
T02	Demographics and Baseline Data Summary Statistics (Safety Population)	X	X
T03	Summary of Study Drug Exposure and Compliance (Safety Population)	X	X
T06	Number and Percent of Subjects with Treatment Emergent Adverse Events (Safety Population)	X	X
T07	Summary of Treatment Emergent Adverse Events (Safety Population)	X	X
T08	Number and Percent of Subjects with Treatment Emergent Serious Adverse Events (Safety Population)	X	X
T09	Number and Percent of Subjects with Treatment Emergent Adverse Events by Relationship to Treatment (Safety Population)	X	X
T10	Number and Percent of Subjects with Treatment Emergent Adverse Events of Grade 2 or Higher (Safety Population)	X	X
T11	Serum Chemistry Clinical Laboratory Summary Statistics by Visit (Safety Population)	X	
T12	Hematology Clinical Laboratory Summary Statistics by Visit (Safety Population)	X	
T13	Urinalysis Clinical Laboratory Summary Statistics by Visit (Safety Population)	X	
T14	Serum Chemistry Shift Table by Visit (Safety Population)	X	
T15	Hematology Shift Table by Visit (Safety Population)	X	
T16	Urinalysis Shift Table by Visit (Safety Population)	X	
T17	Vital Sign Parameters Summary Statistics by Visit (Safety Population)	X	X
T19	Summary of ECG by Assessment Category and Visit (Safety Population)	X	
T20	ECG Shift Table by Assessment Category and Visit (Safety Population)	X	
T21	Number and Percent of Subjects Taking Concomitant Medications by ATC Level 3 and Preferred Term (Safety Population)	X	

4.2 Listings Planned for Interim Reports and Final Study Report

Listing #	Data Listing Title	CSR	DSUR
DL01	Subject Disposition Data Listing	X	X
DL02	Protocol Deviations Data Listing	X	
DL03	Demographics Data Listing	X	
DL05	Prior and Concomitant Medications Data Listing	X	
DL06a	Adverse Events Data Listing	X	X
DL06b	Serious Adverse Events Data Listing	X	
DL06c	Adverse Events with Grade 3 or Higher Data Listing	X	
DL06d	Adverse Events Leading to Study Discontinuation	X	
DL07	Physical Exam Data Listing	X	
DL08	Vital Signs Data Listing	X	X
DL09	ECG Data Listing	X	
DL10	Study Drug Administration Data Listing	X	

DL11	Serum Chemistry Data Listing	X	X
DL12	Hematology Data Listing	X	X
DL13	Urinalysis Data Listing	X	X
DL15	Pregnancy Test Data Listing	X	

5. REFERENCES

Protocol MSK-003: Long Term Safety Study of Amifampridine Phosphate in Patients with MuSK Antibody Positive and AChR Antibody Positive Myasthenia Gravis Patients, amendment to Final v1.0, Catalyst Pharmaceuticals, Inc. February 07, 2020

6. ATTACHMENT: THE SHELLS OF TABLES AND LISTINGS PLANNED FOR INTERIM AND FINAL STUDY REPORTS

Approval for Statistical Analysis Plan

Title:	**Long Term Safety Study of Amifampridine Phosphate in Patients with MuSK Antibody Positive and AChR Antibody Positive Myasthenia Gravis Patients**
Reference:	**MSK-003/SAP**
Version:	**2.0**
Date effective:	
Author:	**Dion Chen, PhD.**

Author's signature: Dion Chen Date: 02/22/2023

The above Statistical Analysis Plan has been reviewed and approved by the Sponsor:

Name of Reviewer/Approver	**Gary Ingenito, MD**
Position:	**Chief Medical Officer, Catalyst Pharmaceuticals, Inc.**

Signature for sponsor: Gary Ingenito Date: 02/22/2023

Name of Reviewer/Approver

Position:

Signature for sponsor: Date:

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SIGNATURE CERTIFICATE

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SIGNERS

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Name Gary Ingenito	**Status** signed	**Viewed At** 02/22/2023 10:29 EST
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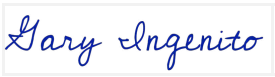
	Typed Signature 	
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AUDITS

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