A Phase 2A Safety and Biomarker Study of EPI-589 in Subjects with Amyotrophic Lateral Sclerosis

Protocol No.: EPI589-15-001

STATISTICAL ANALYSIS PLAN

Version: 1.1
Date: 20-Mar-2018
Biostatistician: [redacted]

Confidentiality Statement

Approval of Statistical Analysis Plan
Protocol No : EPI589-15-001

The undersigned approved the SAP Version 1.1, dated 20-Mar-2018 as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

BioElectron Technology Corporation
Approval:

[redacted] [redacted] 21 MAR 2018

Signature Print Name **Date**

(Title: [redacted] **)**

QPS-Qualitix Approval:

[redacted] [redacted] 22 Mar 2018

Signature [redacted] Print Name **Date**

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1. INTRODUCTION

This is a phase 2a safety and biomarker study of EPI-589 in subjects with amyotrophic lateral sclerosis (ALS). Approximately 20 subjects with amyotrophic lateral sclerosis (ALS) will be enrolled.

This statistical analysis plan (SAP) is based on protocol amendment 1.0, dated 09-Sep-2015. The SAP provides details of data handling procedures and statistical analysis methods for efficacy and safety evaluations. It also outlines statistical programming specifications for tables and listings, and other details on the analyses not provided in the study protocol. It is noted that in case there is discrepancy between the SAP and the protocol then the SAP will supersede the protocol.

This SAP will include efficacy and safety analysis only. The pharmacokinetic (PK) analysis plan is not part of this SAP.

2. STUDY OBJECTIVE

Primary Objective

The primary objective is to evaluate the effects of EPI-589 on safety as assessed by occurrence of drug-related serious adverse events in subjects with ALS.

Secondary Objectives

The secondary objectives are to evaluate the effects of EPI-589 in subjects with ALS on:

(1) Glutathione (redox) cycle biomarkers as measured in blood, cerebral spinal fluid, and urine
(2) Disease progression as assessed by ALS Functional Rating Scale-Revised
(3) Respiratory function as assessed by pulmonary function tests and capnography
(4) Failure to thrive as measured by body weight
(5) Swallowing as assessed by change in water and solid swallowing tests
(6) Speech as assessed by speech evaluation
(7) Muscle function as assessed by handheld dynamometry
(8) Drug plasma concentration measurements
(9) Hematology, blood chemistry, electrocardiogram

3. STUDY DESIGN

This is an open-label, single arm study. After study enrollment, baseline assessments will be performed. Subjects participate in a 30-day run-in phase to establish baseline ALS

disease-related clinical and biomarker features. EPI-589 will then be administered for 3 months, unless discontinued for safety or tolerability issues. All subjects will then be followed for an additional 90 days to determine long-term effects, duration of response to treatment, and potential effects of EPI-589 therapy on known disease trajectory.

3.1 Schedule of Assessments and Dosing Schedule

	-30 Days (± 3 days)	-30 Days (± 3 days)	Day 0	Month 1	Month 2[e]	Month 3	Month 4	Month 5[e]	Month 6
	Screening	Run-in[d]	Baseline	Treatment Phase			Withdrawal Phase		
Informed consent	✓								
Inclusion /Exclusion criteria	✓								
Past Medical history	✓								
Previous tests review	✓								
12-lead ECG	✓		✓	✓		✓			
C-SSRS			✓				✓		
Physical exam, height[a], weight & vital signs	✓[b]		✓	✓		✓	✓		✓
Pulmonary function assessment and Capnography	✓		✓	✓		✓			✓
Serum Chemistry	✓		✓	✓		✓			
Hematology (including coagulation panel)	✓		✓	✓		✓			
Urinalysis	✓								
Pregnancy test[c]	✓		✓	✓		✓			
Enrollment		X							
Blood-based glutathione cycle biomarkers		✓	✓	✓		✓	✓		✓
Urine-based biomarkers		✓	✓	✓		✓	✓		✓
Lumbar puncture (CNS)			✓			✓			
ALSFRS-R		✓	✓	✓		✓	✓		✓
Water and solid swallowing tests			✓			✓			✓
Speech assessment			✓			✓			✓
Handheld dynamometry			✓			✓			✓
AE/SAE Assessment			✓	✓	✓[e]	✓	✓	✓[e]	✓[g]
Drug plasma concentration[f]				✓[f]		✓[f]			
Concomitant medications	✓		✓	✓	✓[e]	✓	✓	✓[e]	✓[g]
Dosing Schedule				**Month 1**	**Month 2**	**Month 3**			
EPI-589 BID				✓	✓	✓			

a. Height measurement need not be repeated after treatment begins.

b. Physical examination includes breast examination in women at screening.

c. Urine or Serum pregnancy test will be done for females of child bearing potential only.

d. Run-in assessments must be performed 30 Days (+/- 3 days) prior to baseline after confirmation of eligibility and enrollment in the study.

e. Month 2 assessments and Withdrawal Phase Month 5 assessments can be conducted by telephone.
f. Samples will be collected at 0-hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose on study visit days.
g. AEs reported at Month 6 (and any associated concomitant medications) must be followed for 30 days; this follow-up may be conducted by telephone

3.2 Primary Endpoint

To evaluate the effects of EPI-589 on safety as assessed by occurrence of drug-related serious adverse events in subjects with ALS following three months of EPI-589 therapy.

3.3 Secondary Endpoints

Secondary Endpoints (Efficacy)
(1) Blood-based biomarkers
(2) CNS-based biomarkers
(3) Urine-based biomarkers
(4) Disease progression as assessed by ALS Functional Rating Scale-Revised
(5) Respiratory function as assessed by pulmonary function tests and capnography
(6) Failure to thrive as measured by body weight
(7) Swallowing as assessed by change in water and solid swallowing tests
(8) Speech as assessed by speech evaluation
(9) Muscle function as assessed by handheld dynamometry
(10) Drug plasma concentration measurements

Secondary Endpoints (Safety)
(1) Routine assessments of AEs and SAEs
(2) Dose limiting toxicities
(3) Routine serum chemistries with liver function tests
(4) Routine hematology tests with coagulation tests
(5) Physical exam and vital signs
(6) 12-lead electrocardiogram
(7) C-SSRS

4. GENERAL STATISTICAL ISSUES

For data listings, all raw data will be displayed exactly as provided. For summaries of quantitative data, the median, minimum and maximum value will be reported exactly as the raw data are reported; measures of central tendency (means will be reported as one decimal more than the raw data and measure of variance (SD) will be reported as the two

decimals more than the raw data.

4.1 Continuous endpoints

Descriptive statistics including number of observation, mean, median, standard deviation, minimum and maximum will be presented for the raw data as well as change from baseline.

4.2 Categorical endpoints

The count and percentages will be used to summarize the categorical data.

4.3 Sample size estimation and power

Approximately 20 subjects will be enrolled in this exploratory biomarker study.

5. DATA HANDLING PROCEDURES

5.1 Coding System

All AEs will be coded according to the MedDRA dictionary, version 15.0 or higher, and be reported by System Organ Class and Preferred Term.

Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary.

5.2 Missing Data Handling

For missing data related to a safety or efficacy endpoint, no missing data method will be performed.

6. ANALYSIS OF STUDY POPULATIONS

In this study, there will be two populations, efficacy intent-to-treat (EITT) population and safety population. The EITT population will be used in the efficacy analysis, and the safety population will be used in the safety analysis. Demographic characteristics will be presented and summarized for all subjects in the EITT population and safety population. No formal statistical comparisons will be made for either the EITT or Safety populations. The populations for analysis applied in this study are defined as follows:

6.1 Efficacy Intent-to-treat (EITT) Population

The efficacy intent-to-treat (EITT) population will consist of any subject receiving at least one dose of EPI-589.

6.2 Safety Population

The safety population will consist of any subject receiving at least one dose of EPI-589.

The analysis of study population will be summarized as Table 14.1.1. Besides, subjects excluded from the analysis will be listed as Listing 16.2.3.

7. DISPOSITION OF PATIENTS AND STUDY COMPLETION

Data on the completion status and primary reason for study discontinuation will be listed in Listing 16.2.1.1 and Listing 16.2.1.2. All subjects' disposition and completion status will be summarized in Table 14.1.1.

Individual subject eligibility will be listed in Listing 16.2.1.3. All protocol deviation(s) will be listed in Listing 16.2.2.

8. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics information will be listed in Listing 16.2.4.1. Demographics information will be summarized in Table 14.1.2.

8.1 Medical History

Medical history and concurrent medical conditions data will be listed by subject in Listing 16.2.4.2.

9. EFFICACY ANALYSIS

9.1 Primary Efficacy Variable

The primary endpoint of this study is to evaluate the effects of EPI-589 on safety as assessed by occurrence of drug-related serious adverse events in subjects with ALS. No primary efficacy variable is defined on protocol.

9.2 Secondary Efficacy Variables

Secondary efficacy endpoints included:
(1) Blood-based biomarkers
The blood-based glutathione (redox) cycle biomarkers will be summarized descriptively at Baseline, Month 1, Month 3, Month 4, Month 6 and change from baseline. The listings of

individual subjects blood-based glutathione (redox) cycle biomarkers will be presented as Listing 16.2.6.1. The summary results will be presented as Table 14.2.1.

(2) CNS-based biomarkers

The CNS-based glutathione (redox) cycle biomarkers will be summarized descriptively at Baseline, Month 3 and change from baseline. The listings of individual subjects CNS-based glutathione (redox) cycle biomarkers will be presented as Listing 16.2.6.2. The summary results will be presented as Table 14.2.2.

(3) Urine-based biomarkers

The Urine-based glutathione (redox) cycle biomarkers will be summarized descriptively at Baseline, Month 1, Month 3, Month 4, Month 6 and change from baseline. The listings of individual subjects urine-based glutathione (redox) cycle biomarkers will be presented as Listing 16.2.6.3. The summary results will be presented as Table 14.2.3.

(4) Disease progression as assessed by ALS Functional Rating Scale-Revised

The ALS Functional Rating Scale (ALSFRS-R) total score will be summarized descriptively at Baseline, Month 1, Month 3, Month 4, Month 6 and change from baseline. The listings of individual subjects ALS Functional Rating Scale (ALSFRS-R) will be presented as Listing 16.2.6.4. The summary results will be presented as Table 14.2.4.

(5) Respiratory function as assessed by pulmonary function tests and capnography

The pulmonary function tests included vital capacity (VC), forced vital capacity (FVC), forced expiratory volume (FEV_1) and maximum inspiratory pressure (MIP); and capnography included respiratory rate (RR), heart rate (HR), SpO_2 and $ETCO_2$. Based on the CRF design, only vital capacity (VC), maximum inspiratory pressure (MIP) and capnography will be analyzed. The pulmonary function is performed from a fast vital capacity (FVC) or slow vital capacity (SVC) maneuver. The vital capacity (VC) will be analyzed as the highest number in % among the SVC or FVC trials. The MIP will be derived as the maximum value in unit cmH_2O of among trials. It will be summarized descriptively at Baseline, Month 1, Month 3, Month 6 and change from baseline. The listings of individual subjects Slow Vital Capacity (SVC) or Fast Vital Capacity (FVC) will be presented as Listing 16.2.6.5; Maximum Inspiratory Pressure (MIP) will be presented as Listing 16.2.6.6; and capnography will be presented as Listing 16.2.6.7. The summary results will be presented as Table 14.2.5.

(6) Failure to thrive as measured by body weight

The failure to thrive as measured by body weight is defined as weight loss of more than 5%

from baseline, and the failure to thrive as measured by body weight will be summarized descriptively at Baseline, Month 1, Month 3, Month 4, Month 6. The listings of individual subjects weight will be presented as Listing 16.2.6.8. The summary results will be presented as Table 14.2.6.

(7) Swallowing as assessed by change in water and solid swallowing tests
The average solid and water swallowing time will be summarized descriptively at Baseline, Month 3, Month 6 and change from baseline. The listings of individual subjects solid and water swallowing tests will be presented as Listing 16.2.6.9 and Listing 16.2.6.10. The summary results of solid and water swallowing tests will be presented as Table 14.2.7.

(8) Speech as assessed by speech evaluation
The speech evaluation will be summarized descriptively at Baseline, Month 3, Month 6 and change from baseline. The listings of individual subjects speech assessment will be presented as Listing 16.2.6.11. The summary results of speech evaluation will be presented as Table 14.2.8.

(9) Muscle function as assessed by handheld dynamometry
The handheld dynamometry will be summarized descriptively at Baseline, Month 3, Month 6 and change from baseline. The listings of individual subjects handheld dynamometry will be presented as Listing 16.2.6.12. The summary results of handheld dynamometry will be presented as Table 14.2.9.

No formal statistical comparisons will be made for all secondary efficacy variables. All secondary endpoints will be summarized descriptively as number of observation, mean, median, standard deviation, minimum and maximum for continuous variables; and count and percentages for categorical variables.

10. EXTENT OF EXPOSURE AND DRUG COMPLIANCE

The dosing compliance and missed dose data be listed by subject in Listing 16.2.5.1 and Listing 16.2.5.2.
Listing 16.2.5.1: Dosing Compliance
Listing 16.2.5.2: Missed Dose

Besides, the drug concentration data will be presented as Listing 16.2.5.4.

11. SAFETY ANALYSIS

11.1 Adverse Events

Clinical AEs will be monitored throughout the study. All AEs, whether observed by the Investigator, reported by the subject, from clinically significant laboratory findings, or other means, will be recorded in the CRF. The listing of all AEs will be provided in Listing 16.2.7.1. The listing of all AEs leading to discontinuation will be provided in Listing 16.2.7.4.

All AEs will be graded if possible by Common Terminology Criteria for Adverse Events (CTCAE) v4.03. The severity of AEs that cannot be graded by CTCAE v4.03 will be categorized as follows:
Grade 1 – Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
Grade 2 – Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
Grade 3 – Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalizations possible.
Grade 4 – Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required hospitalization, life threatening, or hospice care probable.
Grade 5 – Death

Association or relatedness to the study medication will be graded as either “probably”, “possibly”, or “unlikely”. Determination of relatedness includes:
PROBABLY – The adverse event:
1. Follows a reasonable temporal sequence from drug administration
2. Abates upon discontinuation of the drug
3. Cannot be reasonably explained by the known characteristics of the subject’s clinical state

POSSIBLY – The adverse event:
1. Follows a reasonable temporal sequence from drug administration
2. Could have been produced by the subject’s clinical state or by other modes of therapy administered to the subject

UNLIKELY – The adverse event:
1. Does not follow a reasonable temporal sequence from drug administration
2. Is readily explained by the subject’s clinical state or by other modes of therapy administered to the subject

All AEs will be coded by system organ class and preferred term for analysis. Treatment-emergent adverse event (TEAE) is defined as AEs occur after the first administration of study drug, or AEs occur before the first administration of study drug and worsen in severity after first dose. Unless otherwise specified, all adverse event summaries will include the TEAEs only. For purposes of the summary tables, AEs will be classified as either related or not related to study drug. The drug-related AEs are assessed as ' Probably', or 'Possibly' related to study treatment. This summary will present the number and percentage of subjects, as well as number of events.

A general summary of all TEAEs will be provided in Table 14.3.1.1.1 according to the following categories:

- Subject with any AE
- Subject with any SAE
- Subject with any drug-related AE
- Subject with any drug-related SAE

Also, a general summary of all TEAEs will be provided in Table 14.3.1.1.2 according to the following categories:

- CTCAE Grade
- Relationship to Study Medication
- Serious AE
- Dose Limiting Toxicity
- Action Taken with Study Medication

Other summary tables for adverse events will include:
Table 14.3.1.2: Treatment-Emergent Adverse Events - MedDRA
Table 14.3.1.3: Treatment-Emergent Adverse Events by Severity - MedDRA
Table 14.3.1.4: Treatment-Emergent Adverse Events by Relationship to Study Drug and Severity - MedDRA
Table 14.3.1.5: Treatment-Emergent Adverse Events Leading to Discontinuation

11.2 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose results in any of the following:

1. Death
2. A life-threatening adverse drug experience
3. Inpatient hospitalization or prolongation of existing hospitalization
4. A persistent or significant disability/incapacity

5. A congenital anomaly/birth defect
6. Important medical events (ie: bronchospasm, development to drug dependency) that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the serious definition

A listing of all serious adverse events will be provided in Listing 16.2.7.2 and Listing 16.2.7.3, and the summary of SAEs will be presented:
Table 14.3.1.6: Treatment-Emergent Serious Adverse Events - MedDRA
Table 14.3.1.7: Treatment-Emergent Serious Adverse Events by Relationship to Study Drug and Severity - MedDRA

11.3 Laboratory Evaluation

Clinical laboratory tests, including standard hematology, chemistry, urinalysis and pregnancy test:

Hematology

1. Erythrocytes: red blood cell (RBC) count, hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red cell distribution width (RDW)
2. Leukocytes: white blood cell count and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) reported as absolute values
3. Platelets: platelet count, mean platelet volume (MPV)
4. Coagulation: prothrombin time (PT), INR, partial thromboplastin time (PTT).

Serum Chemistry

1. Liver: ALP, ALT (serum glutamic-pyruvic transaminase [SGPT]), AST (serum glutamic-oxaloacetic transaminase [SGOT]), bilirubin (total, direct, and indirect), gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH)
2. Renal: blood urea nitrogen (BUN), creatinine
3. Electrolytes: sodium, potassium, chloride, and carbon dioxide (CO_2 as bicarbonate)
4. General: creatine phosphokinase (CPK), CK fractionated (CK-MB, CK-MM and CK-BB) and troponin (baseline only), protein (total), albumin, calcium, magnesium, glucose, phosphate
5. Lipids: cholesterol (total), high-density lipoprotein (HDL) cholesterol, low-density

lipoprotein (LDL) cholesterol, cholesterol/HDL Ratio (calculated), non-HDL cholesterol (calculated) and triglycerides

The cholesterol/HDL Ratio is calculated as cholesterol (total)/ high-density lipoprotein (HDL) cholesterol; and non-HDL cholesterol is calculated as cholesterol (total) - high-density lipoprotein (HDL) cholesterol.

Urinalysis
The urinalysis items included: Color, Clarity, Specific Gravity, pH, Leukocytes, Blood, Nitrite, Ketones, Bilirubin, Urobilinogen, Protein and Glucose.

Pregnancy Test
Serum or urine human chorionic gonadotropin (HCG), beta subunit, will be performed on all female subjects of childbearing potential at each study visit through to the end of treatment.

By-subject listings of measured values for clinical laboratory test data (hematology, chemistry and urinalysis) will be prepared in Listing 16.2.8.3 ~ Listing 16.2.8.5. A listing of pregnancy test will be provided in Listing 16.2.8.6. Observations outside the normal range will be flagged. The abnormal values will be flagged with 'L' (low) for values below the lower limit of the laboratory's normal range or 'H' (high) for values above the upper limit of the laboratory's normal range. The abnormal values for clinical laboratory test data (hematology, chemistry and urinalysis) will be prepared in Listing 16.2.8.1. The record with observed value of clinical laboratory data below or above the detection limit will be imputed with the detection limit for analysis. The summary results of laboratory assessment (hematology and chemistry) will be presented as Table 14.3.5.1 and Table 14.3.5.2, respectively.

11.4 Vital Signs and Physical Examination

Vital Signs
Individual subject vital signs (height, weight, systolic body pressure, diastolic blood pressure, heart rate, respirations and body temperature) will be listed in Listing 16.4.1.

The observed value of vital signs at Baseline, Month 1, Month 3, Month 4, Month 6 and change from baseline values will be summarized in Table 14.3.6.

Physical Exam
Physical exam data will be listed in Listing 16.4.2, and will be summarized for Baseline, Month 1, Month 3, Month 4, Month 6 in Table 14.3.7.

11.5 Other Variables Related to Safety

Concomitant Medications

Individual subject concomitant medications will be listed in Listing 16.2.5.3.

12-Lead ECG

Individual subject 12-Lead ECG data (heart rate, PR interval, RR interval, QRS duration, QT, QTc (Bazette) and overall interpretation) will be listed in Listing 16.4.3, and will be summarized at Baseline, Month 1, Month 3 and change from baseline in Table 14.3.8.

Columbia Suicide Severity Rating Scale (C-SSRS)

Individual subject Columbia Suicide Severity Rating Scale (C-SSRS) data will be listed in Listing 16.4.4, and will be summarized as suicidal ideation and suicidal behavior in Table 14.3.9.1. In addition, the Columbia Suicide Severity Rating Scale (C-SSRS) shift table will be provided as Table 14.3.9.2.

Telephone Contact

Individual subject telephone Contact data will be listed in Listing 16.4.5.

12. COMPUTER METHODS

All statistical analyses will be conducted using SAS® software, Version 9.3 of the SAS System for Windows 7. Copyright© 2013 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.