EPI589-15-001

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

Original Protocol:	24 March 2015
Protocol Amendment 1.0:	09 September 2015
Protocol Amendment 2.0:	17 February 2017

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I. PROTOCOL SYNOPSIS

Title of study	A Phase 2A Safety and Biomarker Study of EPI-589 in Subjects with Amyotrophic Lateral Sclerosis
Protocol number	EPI589-15-001
IND Number	126,276
Original protocol date	24 March 2015
Protocol Amendment 1.0 date	09 September 2015
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Name of sponsor/company	BioElectron Technology Corporation 350 North Bernardo Ave Mountain View CA 94043
Sponsor contact	[redacted] Office: [redacted]
Name and affiliation of Principal Investigator	[redacted]
Name of active ingredient	EPI-589
Phase of development	Phase 2a
Study population	Approximately 20 subjects with amyotrophic lateral sclerosis (ALS)
Rationale for study	ALS is a disorder characterized by high levels of oxidative stress. High levels of oxidative stress (OS) biomarkers have been measured in patients with ALS relative to age-matched unaffected controls. The high levels of OS are thought to be key pathogenic factors in disease progression. Reduced glutathione is an essential intermediary metabolite that serves as the primary native cellular antioxidant. Reduced glutathione (GSH) serves as the cell's primary defense against reactive oxygen species (ROS); however, in diseases characterized by high levels of oxidative stress, ROS production outstrips the

	available supply of GSH resulting in depletion of GSH and ROS-mediated cell injury and death. Altered levels of GSH have been recorded in the central nervous system (CNS) of patients with ALS. EPI-589 targets enzymes critical to the synthesis of GSH. In adult healthy volunteer studies, EPI-589 increased levels of GSH and other GSH-related sulfur analytes. EPI-589 rescues ALS patient cells from oxidative stress-induced cell death. In a phenotypic assay system, EPI-589 is a redox active molecule that has demonstrated potency (EC50 <100nM) and efficacy (>80% rescue from oxidative stress-induced cell death).
Study objective(s)	Primary Objective 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 To evaluate the effects of EPI-589 in subjects with ALS on: 1. Glutathione 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 hand-held dynamometry 8. Drug plasma concentration measurements 9. Hematology, blood chemistry, electrocardiogram
Study design	Open label with 30-day run-in phase to establish baseline parameters and a 90-day withdrawal phase to determine duration of treatment response.
Study duration	Run-in phase: 1 month Treatment phase: 3 months Withdrawal phase: 3 months
Planned number of subjects	Approximately 20 subjects

Test product, mode of administration, strength, and dose	Test Product EPI-589 in a tablet formulation at a strength of 250 mg Mode of Administration Oral with food Dose EPI-589 500 mg BID
Reference therapy (for controlled studies)	None
Safety monitoring	Clinical 1. Physical exam and vital signs 2. Evaluation of adverse events 3. 12-lead Electrocardiogram 4. Columbia Suicide Severity Rating Scale (C-SSRS) Laboratory 1. Routine serum chemistries 2. Routine hematology tests and coagulation tests
Inclusion Criteria	1. Diagnosis of possible, probable, laboratory supported probable or definite amyotrophic lateral sclerosis (ALS) by El Escorial Criteria 2. [redacted] or [redacted] between 21 and 70 years of age 3. Forced vital capacity (FVC) ≥ 70% of predicted 4. Onset of weakness within 3 years as documented in clinical records 5. Agreement to use contraception if within reproductive years 6. Willingness and ability to comply with study procedures 7. Stable regimen of dietary supplements for 30 days prior to enrollment 8. Abstention from use of other investigative or non-approved drugs 9. Subjects on riluzole must be on a stable dose for at least 30 days prior to study enrollment. 10. Subject must be able to swallow 0.375 x 0.700 inch tablets.
Exclusion Criteria	1. Allergy to EPI-589 2. Use of invasive or non-invasive ventilation 3. Participation in other intervention studies 4. Diagnosis of any other neurologic disease 5. Malignancy within past two years 6. Pregnant or plans to become pregnant

	7. History of stroke 8. History of brain surgery 9. Hepatic insufficiency with liver function tests (LFTs) greater than three times upper limit of normal (ULN) 10. Renal insufficiency requiring dialysis 11. End stage cardiac failure 12. Participation in a trial of a device, drug or other therapy for ALS within 3 months of screening and for the duration of the trial
Treatment	Following study enrollment, subjects will 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. Following cessation of therapy, subjects will return to the clinic for assessments at two time points during the 90-day withdrawal period.
Efficacy variables	1. Blood glutathione cycle biomarkers 2. CNS biomarkers 3. Urine biomarkers 4. ALS Functional Rating Scale-Revised 5. Pulmonary function tests (FVC, FEV_1, VC, MIP) 6. Capnography (CO_2, respiratory rate, oxygen saturation) 7. Solid and liquid swallowing tests 8. Speech 9. Muscle function 10. Body weight
Safety variables	<u>Clinical</u> 1. Routine assessments of AEs and SAEs 2. Dose limiting toxicities 3. Electrocardiogram 4. C-SSRS <u>Laboratory</u> 1. Routine serum chemistries with liver function tests 2. Routine hematology tests with coagulation tests
Safety monitoring	<u>Clinical</u> Physical exam and vital signs Evaluation of adverse events <u>Laboratory</u> PT/PTT Standard blood and serum chemistries

	12-lead Electrocardiogram
Statistical Considerations	Data Analysis This is a subject-controlled open-label study to determine the safety and tolerability of EPI-589 in subjects with ALS as well as to determine if EPI-589 can alter the biochemical signature of ALS as assessed by peripheral blood biomarkers, CNS biomarkers, and urine biomarkers. In addition, data will be collected on a number of disease-relevant clinical measures of disease progression, and assessments by the ALS Functional Rating Scale-Revised (ALSFRS-R) will be compared with historical control data.

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II. 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	✓		✓[h]	✓		✓			
Hematology (including coagulation panel)	✓		✓[h]	✓		✓			
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 [redacted] 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. 12 hour PK can be obtained at time 0.
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
h. Screening values can be used if done within one month of baseline and if completed under fasted conditions

III. BACKGROUND INFORMATION AND RATIONALE

A. Overview of Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease without an effective therapy. ALS causes progressive damage and loss of motor neurons in the central and peripheral nervous systems that result in a gradual decrease and loss of motor and brainstem function. ALS is estimated to occur in 1–2/100,000 people worldwide. The majority of ALS cases are sporadic, however about 10% of cases are inherited (familial ALS), with 20% of familial ALS resulting from mutant forms of the superoxide dismutase soluble gene (SOD1), a homodimer that converts superoxide radicals to molecular oxygen in mitochondrial membranes and cytoplasm. Symptoms of motor neuron death in sporadic and familial ALS are clinically indistinguishable. The role of oxidative stress (OS) and mitochondrial dysfunction as key pathophysiological features in all forms of ALS has been well established.[1]

ALS is typically diagnosed between age 50 and 60. The earliest symptoms are muscle weakness and atrophy. Other presenting symptoms include muscle cramping, difficulty swallowing and altered or slurred speech. Average survival time following diagnosis is 3 to 4 years. Patients experience increasing difficulty with movement, dysphagia, dysarthria, and respiratory failure requiring chronic ventilatory or other respiratory assistive support. Most patients with ALS die from respiratory failure or pneumonia.

The only approved treatment for ALS is riluzole (Rilutek®), which acts by inhibiting the release of glutamate in the central nervous system. Riluzole has been shown to extend survival by 2 to 3 months. The mainstay of treatment for ALS is symptomatic: physical therapy in the early stages of the disease, and therapies that address oropharyngeal and psychological symptoms, motor and respiratory function, and pain.

The importance of OS and mitochondrial pathology in ALS pathology is well substantiated.[2,3] OS occurs when the level of reactive oxygen species (ROS) formed from biological processes exceeds the supply of native antioxidants. Patients with SOD1 mutations have a clear genetic link to oxidative stress susceptibility given the role of superoxide dismutase in modulating OS.[4] However, OS is present in all forms of ALS.[5] Pathological studies on postmortem ALS patient tissue have demonstrated increased levels of OS including elevated protein carbonyl levels in the spinal cord and motor cortex.[5,6] In addition, elevated levels of OS biomarkers have been detected in the cerebrospinal fluid (CSF) of ALS patients including 8-hydroxy-2'-deoxyguanosine and 4-hydroxynonenal.[7,8,9,10] In addition, studies using magnetic resonance spectroscopy (MRS) have demonstrated that levels of reduced glutathione (GSH)—a critical component of the cellular antioxidant system—are more than 30% lower in patients with ALS compared to healthy volunteers,[11] supporting the involvement of OS in the brain with disease pathology.

There is evidence of mitochondrial structure, genetic and biochemical abnormalities in patients with ALS. A number of studies have demonstrated decreased activity in mitochondrial

complexes that form the electron transport chain and muscle biopsies from patients with ALS demonstrate abnormal morphology: abnormal size, paracrystalline inclusions and abnormal cristae.[12,13] The motor cortex and spinal cords of patients with ALS have also been found to have a higher frequency of mitochondrial DNA(mtDNA) mutations compared to controls.[14,15]

B. Rationale for the Study of EPI589-15-001 in Subjects with ALS

Reduced glutathione (GSH) is an essential intermediary metabolite that serves as the primary native cellular antioxidant, and the cell's primary defense against ROS. In diseases characterized by high levels of OS, ROS production outstrips the available supply of GSH resulting in depletion of GSH and ROS-mediated cell injury and cell death.

EPI-589 is a novel redox active therapeutic being developed by BioElectron Technology Corporation for the treatment of diseases in which OS plays a critical role. EPI-589 acts to catalytically increase levels of GSH by targeting key enzymes in the glutathione synthesis pathway. In in vitro studies, EPI-589 has been shown to replenish levels of GSH and protect against OS-induced cell death. In addition, in adult healthy volunteers, EPI-589 has been found to augment levels of GSH and related sulfur analytes.

Given the strong evidence of GSH depletion and OS in the pathogenesis of ALS,[16,17] EPI-589 may hold promise as a therapeutic for patients with ALS. The purpose of this study is to confirm target engagement of EPI-589 in adult patients with ALS by studying peripheral and central nervous system (CNS) glutathione cycle biomarkers.

C. Name and Description of Investigational Product

EPI-589 is (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dien-1-yl)butanamide. A common chemical name of EPI-589 is (R)-troloxamide quinone. EPI-589 is manufactured from the (R)-Trolox® enantiomer, and is a pale yellow to yellow solid. The EPI-589 drug product is an immediate release film-coated tablet at a 250-mg dosage strength. The tablet is oval shaped and yellow.

The Investigator will ensure that all study drugs are stored and dispensed in accordance with the Food and Drug Administration (FDA) and local regulations concerning the storage and administration of investigational drugs.

D. Findings from Non-Clinical and Clinical Studies

D1. Non-Clinical Studies

EPI-589 is an orally available compound that has been demonstrated in vitro and in vivo to cross the blood-brain-barrier. 28-day and 3-month repeat-dose toxicity studies in rat and monkey showed a No Observed Adverse Effect Level (NOAEL) of 300 mg/kg/day, corresponding to

combined mean C_{max} values of 37,717 – 56,500 ng/mL (rat) and 14,300 – 16,417 ng/mL (monkey), and combined mean AUC_{last} values of 149,495 – 297,000 ng.h/mL (rat) and 47,300 – 67,656 ng.h/mL (monkey).

Exposure to 1,000 mg/kg/day EPI-589 oral dosing (PO) induced hematology changes in the rat and induced toxicity resulting in death or euthanasia in the monkey. Rats exposed to 1,000 mg/kg/day PO EPI-589 for 28 days showed test-article related effects on hematology parameters consistent with hemolysis and bone marrow regeneration; mild to moderately enlarged spleens; and increased organ weights with some organs possessing corresponding microscopic pathology. The majority of these findings were resolved following the 28-day recovery period. Rats exposed to ≥ 100 mg/kg/day PO EPI-589 exhibited mild effects on hematology parameters consistent with hemolysis and bone marrow regeneration. These findings were not considered adverse. Monkeys exposed to 1,000 mg/kg/day PO EPI-589 for 28 days showed significant test-article related morbidity including elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and microscopic findings in the kidney, liver, skeletal muscle, heart, and lymphoid tissue. In several of the animals the primary cause of morbidity was determined to be test-article related renal tubular degeneration/necrosis.

A fertility study in rat demonstrated that EPI-589 did not produce reproductive toxicity at doses up to 1,000 mg/kg/day. Embryo fetal development studies in rat and rabbit demonstrated the NOAEL for EPI-589 for developmental toxicity to be 300 mg/kg/day. EPI-589 induced toxicity at 1,000 mg/kg/day in rat and rabbit. Findings in the rat included decreased maternal body weights, decreased food consumption, and decreased fetal body weights. There was no teratogenic potential in rat at doses up to 1,000 mg/kg/day. Findings in rabbit included decreased maternal body weights, decreased food consumption, decreased number of viable fetuses, decreased litter size, increased postimplantation loss, increased resorptions (early and late), and increased fetal skeletal malformations. The margin of exposure between healthy humans exposed to 500 mg BID EPI-589 (relevant clinical dose) for 14 days and rabbits is approximately 179- to 236-fold at 1,000 mg/kg/day and 47- to 50-fold at 300 mg/kg/day. Based on these data, EPI-589 is not anticipated to increase the risk of adverse developmental or reproductive outcomes in humans when used in accordance with dosing information.

EPI-589 was negative for mutagenic response in the in vitro Ames bacterial reverse mutation assay; equivocal for the induction of structural and negative for the induction of numerical chromosomal aberrations in the in vitro chromosome aberration assay in Chinese hamster ovary (CHO) cells; and negative in the in vivo micronucleus assay in rat. These data indicate a low clinical mutagenicity risk.

Primary pharmacodynamics studies have demonstrated that EPI-589 is a potent rescue agent in in vitro cellular models of mitochondrial disorders and diseases characterized by mitochondrial pathology and high levels of oxidative stress. The cellular activity of EPI-589 involves a redox-dependent mechanism of action. Secondary pharmacodynamics in vitro studies have shown that EPI-589 does not significantly affect off-target molecular targets. Safety pharmacology metrics

evaluated during the 28-day and 3-month repeat-dose toxicology studies in monkey demonstrated that EPI-589 does not affect cardiovascular in vitro hERG K+ channel current or electrocardiogram (ECG) parameters. EPI-589 does not change respiratory function or adversely impact neurobehavioral function in rat.

Single dose exposure pharmacokinetics studies have demonstrated that EPI-589 is absorbed rapidly in all species with mean T_{max} values ranging from .08 to 1 hour and mean $T_{1/2}$ values ranging from 3.7 to 5.0 hours. In vitro studies suggest that EPI-589 does not significantly inhibit or induce CYP450 enzymes.

D2. Clinical Studies

Safety

Phase I Study EPI589-13-022 evaluated the pharmacokinetics (PK), safety and tolerability of single ascending oral doses (SAD) of EPI-589 in healthy subjects and a preliminary evaluation of safety and tolerability data was performed. No severe or serious adverse events were observed. In total, 15 out of 32 subjects experienced 23 adverse events (AEs). Fourteen of 15 AEs were considered to be related to the study medication by the Investigator. All AEs were of mild intensity and of limited duration. None of the vital signs, ECG parameters or clinical laboratory test results showed a clinically relevant change compared to baseline. From all preliminary data available from this SAD study it may be concluded that there is no objection to proceed with treatment with 50 mg, 100 mg, 250 mg or 500 mg of EPI-589.

Phase I Study EPI589-14-01 evaluated the pharmacokinetics, safety and tolerability of multiple ascending oral doses (MAD) of EPI-589 in healthy subjects, and an evaluation of safety and tolerability data was performed. No severe or serious adverse events were observed. In total, 34 out of 50 subjects experienced 44 AEs. Twenty-four of 34 AEs were considered by the Investigator to be related to the study medication. All but one AE was of mild intensity and of limited duration. A single event of moderate intensity and limited duration was reported: brain contusion (not related) in the 250 mg twice-daily (BID) cohort. None of the vital signs, ECG parameters or clinical laboratory test results showed a clinically relevant change compared to baseline.

E. Human Pharmacokinetics

In MAD study EPI589-14-001, EPI-589 was rapidly absorbed following oral administration and the median C_{max} was attained within 1 hour (0.50 to 0.76 hours) under fasted conditions after single or multiple dosing among these five cohorts. The mean half-life of EPI-589 ranged from 5.64 to 8.47 hours among these five cohorts. In general, the mean values of the time to peak concentration (T_{max}), half-life ($t_{½}$), apparent terminal constant (λz), accumulation ratio (AR), percent fluctuation (%F) and accumulation index (AI) of EPI-589 were similar among the five cohorts.

It appears that no significant effects of age and smoking on EPI-589 pharmacokinetics were observed in this study.

Dose proportionality existed in the exposures ($AUC_{0\text{-}tau}$, C_{max}, C_{min} and C_{avg}) over the dose range of 250 to 500 mg BID EPI-589 under fasted conditions.

F. Clinical Study

EPI589-15-001: A Phase 2A Safety and Biomarker Study of EPI-589 in Subjects with Amyotrophic Lateral Sclerosis.

G. Selection of Drugs and Dosages

The study drug in this trial is EPI-589 (common chemical name (R)-troloxamide quinone).

Each tablet contains 250 mg of EPI-589. The study dose is 500 mg BID, to be maintained in the absence of treatment-emergent toxicity. EPI-589 tablets must be taken with food.

H. Number of Subjects to Enroll in Study

Approximately 20 subjects with ALS.

I. Compliance Statement

This study will be conducted in full accordance with all applicable research policies and procedures, all applicable US federal and local laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312 and 314, and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization (ICH). Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, obtain consent and report AEs in accordance with local institutional policies and procedures and all EU and US federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

J. Relevant Literature and Data

Literature references have been provided in Section XV. Additional information can be found in the Investigator's Brochure.

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IV. STUDY OBJECTIVES

A. 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.

B. Secondary Objectives

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

1. Glutathione 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

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V. INVESTIGATIONAL PLAN

A. General Schema of Study Design

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.

A1. Screening Phase

Suitable candidates for the trial will receive a short overview of the study by the Investigator's staff and, if interested, will undergo Screening. The Investigator will inform each prospective subject of the nature and details of the study, explain the potential risks and must obtain written informed consent from the subject or their legally authorized representative prior to performing any study related procedures.

A2. 30-Day Run-in Phase

Once eligibility is confirmed, the subject will be enrolled in the study and the ALS Functional Rating Scale-Revised (ALSFRS-R) measurements and CNS, urine-based and blood-based glutathione cycle biomarkers, will be collected.

A3. Baseline

ALSFRS-R, lumbar puncture, swallowing, speech, handheld dynamometry, blood-based biomarkers, urine biomarkers, and clinical measurements will be collected.

A4. Treatment Phase

EPI-589 dosing will start on Day 1. Subjects will self-administer EPI-589 at a dose of 500 mg BID.

Blood biomarker, urine biomarker, clinical measurements, and pharmacokinetic plasma concentrations will be collected at Day 29 (+/-3 days) and Day 85 (+/- 3 days). Lumbar puncture will be collected at Day 85 (+/- 3 days).

A5. Study Withdrawal Phase

Closeout data will be collected over a 90-day period, during the Withdrawal Phase.

ALSFRS-R, blood-based biomarkers, urine-based biomarkers, and physical exam including weight and vital signs will be collected at Month 4.

ALSFRS-R, swallowing, speech, handheld dynamometry, blood-based biomarkers, urine-based biomarkers, and physical exam including weight and vital signs will be collected at Month 6.

Adverse events reported as ongoing during the Withdrawal Phase, and any concomitant medications associated with such events will be followed for 30 days. Month 5 AE and concomitant medication assessments can be conducted by telephone.

B. Randomization and Blinding

This is an open-label study.

C. Study Duration, Enrollment and Number of Sites

C1. Duration of Subject Treatment

Subjects will 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. Subjects will return to the clinic for assessments at two time points during a 90-day withdrawal period.

C2. Total Number of Study Sites/Total Number of Subjects Projected

This study will be conducted at the California Pacific Medical Center, San Francisco, CA. Additional sites may be added in order to decrease enrollment timelines.

Projected enrollment is approximately 20 subjects with ALS.

D. Study Population

D1. Inclusion Criteria

1. Diagnosis of possible, probable, laboratory supported probable or definite amyotrophic lateral sclerosis (ALS) by El Escorial Criteria.
2. Male or female between 21 and 70 years of age
3. Forced vital capacity (FVC) ≥ 70% of predicted
4. Onset of weakness within 3 years as documented in clinical records
5. Agreement to use contraception if within reproductive years
6. Willingness and ability to comply with study procedures
7. Stable regimen of dietary supplements for 30 days prior to enrollment
8. Abstention from use of other investigative or non-approved drugs
9. Subjects on riluzole must be on a stable dose for at least 30 days prior to study enrollment.
10. Subject must be able to swallow 0.375 x 0.700 inch tablets.

D2. Exclusion Criteria

1. Allergy to EPI-589
2. Use of invasive or non-invasive ventilation
3. Participation in other intervention studies
4. Diagnosis of any other neurologic disease
5. Malignancy within past two years
6. Pregnant or plans to become pregnant
7. History of stroke
8. History of brain surgery
9. Hepatic insufficiency with liver function tests (LFTs) greater than three times upper limit of normal (ULN)
10. Renal insufficiency requiring dialysis
11. End stage cardiac failure
12. Participation in a trial of a device, drug or other therapy for ALS within 3 months of screening and for the duration of the trial.

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VI. STUDY PROCEDURES

A. Screening (-30 days ± 3 days) Visit

A1. Screening

The Investigator will inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent from the subject prior to performing any study-related procedures and prior to the administration of study drug. Screening evaluations consist of the following:

1. Assessment of eligibility
2. Medical history, chart review
3. Physical examination (including breast examination for women)
4. Height, weight and vital signs
5. Receipt and review of all previous testing
6. 12-lead ECG
7. Pulmonary function assessment
8. Hematology including coagulation, serum chemistry, urine analysis
9. Pregnancy test (women of childbearing potential must have a negative serum or urine pregnancy test)
10. Concomitant medication assessment (last 60 days prior to enrollment)

A2. Run-in Assessments

Run-in assessments must be performed 30 days (+/- 3 days) prior to baseline after eligibility is confirmed and subject is enrolled in the study. Run-in evaluations consist of the following:

1. ALS Functional Rating Scale-Revised
2. Blood-based glutathione cycle biomarkers
3. Urine-based glutathione cycle biomarkers

B. Treatment Phase

If the subject is eligible for the study following all screening procedures and is still willing to participate in the study, the subject must return to the clinic 30 days (+/- 3 days) for baseline assessments. In-clinic study visits are scheduled at Month 1 and Month 3. Month 2 assessments can be conducted via telephone. End of treatment will be at the Month 3 study visit. Pharmacokinetic sampling takes place at Month 1 and Month 3.

B1. Baseline Assessments

The following will be assessed or performed at this visit:

1. Physical examination
2. 12-Lead ECG
3. Pulmonary function assessment and capnography
4. Hematology including coagulation and serum chemistry*
5. Weight and vital signs
6. Pregnancy test (women of childbearing potential)
7. Glutathione cycle blood, urine and CNS biomarkers
8. C-SSRS
9. ALS Functional Rating Scale-Revised
10. Water and solid swallowing tests
11. Speech assessment
12. Handheld dynamometry

EPI-589 will be dispensed to the subjects along with the dosing diary. Subjects will self-administer EPI-589 at a dose of 500 mg BID starting from Day 1.
* Screening values can be used if done within one month of baseline and if completed under fasted conditions

B2. Study Visit Assessments

Adverse events and concomitant medication information will be reviewed and assessed at each visit.

Clinic Visits: Month 1 and Month 3

The following will be assessed or performed at the Month 1 (Day 29 +/-3 days) clinic visit:

1. Physical examination
2. 12-lead ECG
3. Pulmonary function assessment and capnography
4. Hematology including coagulation and serum chemistry
5. Weight and vital signs
6. Pregnancy test (women of childbearing potential)
7. Glutathione cycle blood, urine, and CNS biomarkers
8. ALS Functional Rating Scale-Revised
9. Drug plasma concentration measurements*

The following will be performed at the Month 3 (Day 85 +/- 3 days) clinic visit:

1. Physical examination
2. 12-lead ECG
3. Pulmonary function assessment and capnography
4. Hematology including coagulation and serum chemistry
5. Weight and vital signs
6. Pregnancy test (women of childbearing potential)
7. Glutathione cycle blood, urine, and CNS biomarkers
8. Drug plasma concentration measurements*
9. ALS Functional Rating Scale-Revised
10. Water and solid swallowing tests
11. Speech assessment
12. Handheld dynamometry

*Pharmacokinetics: Plasma concentration samples will be collected at 0-hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose at the Month 1 and Month 3 clinic visits.

Drug accountability and compliance: Subjects should bring the study medication and the dosing diary at the Month 1 and Month 3 visits. All the used and unused study medication should be returned and reconciled at the Month 3 visit.

Month 2 Assessments

Month 2 assessments can be conducted by telephone and will include review of concomitant medications and AEs.

B3. Early Termination of Study Medication

Subjects who terminate from the study after receiving first dose and prior to the completion of the treatment phase should have an end of study visit as soon as possible. All the Month 3 visit assessments should be completed at this visit.

C. Withdrawal Phase and Study Completion

Month 4 Clinic Visit (Day 113 +/- 1 Week)

1. Physical examination
2. Weight and vital signs
3. Blood-based biomarkers
4. Urine-based biomarkers
5. C-SSRS
6. ALS Functional Rating Scale-Revised
7. AEs and SAEs
8. Concomitant medications

Month 5 Assessments

Month 5 assessments may be conducted by telephone.

1. AEs and SAEs
2. Concomitant medications

Month 6 Clinic Visit (Day 169 +/- 1 Week)

1. Physical examination
2. Weight and vital signs
3. Glutathione cycle blood-based biomarkers
4. Glutathione cycle urine-based biomarkers
5. ALS Functional Rating Scale-Revised
6. Water and solid swallowing tests
7. Speech assessment
8. Handheld dynamometry
9. Pulmonary function tests and capnography
10. AEs and SAEs
11. Concomitant medications

Subjects who have an ongoing AE at the time of study completion will be followed for up to 30 days, until the event resolves, or until the Sponsor and the Investigator agree that further follow-up is not medically necessary.

D. Unscheduled Visits

If a subject returns to the clinic outside of the normal treatment visit windows, assessments will be made at the Investigator's discretion. All relevant unscheduled visit data will be recorded in the CRF using the supplemental visit CRF pages.

E. Concomitant Medication

Any medication taken by a subject $\leq$ 60 days prior to enrollment and during the course of the study and the reason for use of the medication will be recorded on the case report form (CRF). During screening, each subject will be instructed to report the use of any medication to the Investigator. Subjects will also be instructed about the importance of not taking any medication throughout the study (including over-the-counter [OTC] medications) without first consulting the Investigator.

F. Prohibited Medications

The following are prohibited while the subject is on study treatment:

1. Use of antioxidants, specifically vitamins E and C beyond the recommended daily allowance
2. Participation 3 months prior to the Screening Visit and for the duration of study in a trial of a device, drug or other therapy for ALS

G. Subject Withdrawals

Subjects may be withdrawn from the study at any time for reasons including the following:

1. At their own request or at the request of their legally authorized representative
2. If, in the Investigator's opinion, continuation in the study would be detrimental to the subject's well-being
3. For failure to comply with the Protocol (i.e., dosing compliance, failure to complete diaries as instructed, failure to keep scheduled appointments)
4. At the specific request of the Sponsor (or designee).
5. Additional protocol specific reasons

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records. If the reason is not known, the subject must be followed to establish whether the reason was due to an AE and, if so, this must be reported in accordance with the procedures in Section X.B.

Evaluations must be performed on all subjects who participate but do not complete the study according to protocol. Dropouts may be replaced at the request of the Sponsor. The Investigator will make every effort to contact subjects lost to follow-up.

Every effort will be made to follow subjects who have an ongoing AE at the time of withdrawal until the event resolves, or until the Sponsor and the Investigator agree that further follow-up is not medically necessary.

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VII. STUDY ENDPOINTS AND EVALUATIONS

A. 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.

B. 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

C. 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

C1. Safety Evaluations

a. Physical Examination

Complete physical exams will be conducted (excluding genital/rectal exam) at screening and baseline. The physical examination will consist of an examination of the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest (including breast examination in women at Screening), heart, abdomen, and extremities.

Medical history and demographics including age, gender, race, height and weight will be collected at Screening.

b. Vital Signs

Vital sign measurements (pulse rate, blood pressure and respiration rate) will be obtained in the sitting position (after the subject has been sitting for five minutes).

Weight (kg) will be assessed in ordinary indoor clothing (i.e., street clothes, scrubs, etc.). Weight and height (cm) will be recorded at Baseline. If clinically significant findings, as determined by the Investigator, are recorded for a particular symptom, sign or abnormal measurement, that measurement will be repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

c. Laboratory Evaluations and Sample Shipment

Each subject will have less than 100 mL of blood drawn over the course of the study.

The following variables will be collected at various times (as detailed in Section II) to assess safety.

d. 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).

e. 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

f. Pregnancy Test

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

Diagnoses associated with any NIH Common Toxicity Criteria (CTC) v4.03 Grade 3 or 4 laboratory abnormalities will be recorded as AEs on the CRF. Repeated and verified laboratory tests that meet at least Grade 3 AE requirements will be reported to the institutional review board (IRB) per institutional requirements. The recorded AEs should indicate the underlying abnormality or diagnosis (e.g., renal insufficiency) if known, as opposed to the observed deviation in laboratory results (e.g., elevated creatinine). Any additional relevant laboratory results obtained by the Investigator during the study will be supplied to the Sponsor.

Laboratory tests that result in significantly abnormal values should be repeated for verification. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. In particular, if a clinically significant abnormal result is observed that is not resolved by the final study visit, repeat tests should be performed to document resolution or stability of the abnormality.

D. Sample Collection Procedures, Bioanalytical Methods and Sample Shipment

Urine, cerebral spinal fluid, and fasting blood samples will be collected for determination of levels of glutathione cycle markers. Additional information about the collection, handling, storage, and shipment of the glutathione cycle marker samples will be provided separately prior to start of the study.

E. Efficacy Evaluations

E1. Glutathione

Blood, urine, and cerebral spinal fluid levels of oxidized glutathione (GSSH) and reduced glutathione (GSH) as well as glutathione metabolites will be used to evaluate EPI-589 target engagement and ability to correct key biochemical aspects of disease pathology.

E2. ALS Functional Rating Scale-Revised (ALSFRS-R)

The ALS Functional Rating Scale–Revised (ALSFRS-R) is a quickly administered (five minutes) ordinal rating scale that assesses patients' capability and independence in 12 functional activities. All 12 activities, six bulbar-respiratory functions, three upper extremity functions (writing, cutting food, and dressing), two lower-extremity functions (walking and climbing), and one other function (turning in bed), are relevant in ALS. Each activity is recorded to the closest approximation from a list of 5 choices, scored 0-4, with the total score ranging from 48 (normal function) to 0 (unable to attempt the task). The ALSFRS has been used extensively in previous clinical trials and validity has been established by correlating ALSFRS scores with quantitative strength testing and changes in strength over time. The ALSFRS-R, which incorporates separate assessment of respiratory function, is validated.

E3. Pulmonary Function Tests and Capnography

Pulmonary function tests will assess vital capacity (VC), forced vital capacity (FVC), forced expiratory volume (FEV_1) and maximum inspiratory pressure (MIP). Capnography will assess end tidal CO_2, oxygen saturation, respiratory rate and heart rate and will be performed in both the upright and supine positions.

E4. Water and Solid Swallowing Tests

Subjects will be observed and timed swallowing water as well as solid foods in accordance with a standardized protocol.

E5. Speech Assessment

Speech will be assessed through a perceptual assessment of overall intelligibility, vocal quality, and other factors by a speech language pathologist.

E6. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a semi-structured tool for assessing suicidal ideation (Questions 1-5) and behavior (Questions 6-10) through a series of questions.

E7. Handheld Dynamometry (HHD)

The strength of designated muscle groups will be measured using handheld dynamometry (HHD). Upper extremity and lower extremity values will be calculated to create overall scores for upper and lower extremity muscles.

VIII. STATISTICAL CONSIDERATIONS

A. Statistical Analysis

In this subject-controlled, open label study the incidence of drug related SAEs in addition to changes from baseline to Month 3 for disease-relevant peripheral and CNS biomarkers as well as clinical measures will be calculated for each subject. In addition, changes in the ALSFRS-R will be measured three months following withdrawal of therapy and compared with disease natural history data to determine effects of EPI-589 on disease trajectory.

A1. Analysis Populations

Demographic characteristics and baseline efficacy data will be presented and summarized for all subjects in the efficacy intent-to-treat (EITT) population. Demographic information will also be summarized for the safety population. No formal statistical comparisons will be made for either the EITT or Safety populations.

B. Efficacy Analysis

B1. Efficacy Variables

The efficacy variables in this study are

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

C. Safety Analysis

The primary objective of this study is to evaluate the effects of EPI-589 safety as assessed by occurrence of drug-related serious adverse events in subjects with ALS. Assessment of safety will include calculating the overall number of subjects (by absolute number and percentage) with a particular AE. Safety will also be evaluated through examining clinical laboratory data (including chemistry and hematology and coagulation information) and physical examination findings, including vital signs obtained throughout the course of the study. A medical monitor will provide study oversight.

D. Sample Size

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

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IX. STUDY MEDICATION

A. Description

EPI-589 is presented as an instant release solid oral tablet. Each tablet contains 250 mg of EPI-589 and the following compendial excipients: lactose monohydrate, microcrystalline cellulose, polyvinylpyrrolidone, crospovidone, and magnesium stearate. Each tablet is film-coated with Opadry® II yellow. The tablets are yellow-colored and oval shaped with a total target weight of 824 mg. The tablets are packaged at 28 tablets per bottle in high density polyethylene (HDPE) pharmaceutical wide mouth containers, induction sealed, and closed with a child resistant closure. Each container is labeled with appropriate product information meeting current regulatory requirements.

B. Packaging

B1. Labeling

Each container is labeled with appropriate product information meeting current regulatory requirements that comply with 21 CRF 312.6.

B2. Dosage Form

The EPI-589 drug product will be provided in a 250-mg tablet formulation.

B3. Dispensing

Tablets are packaged in white round HDPE wide mouth containers. Each container holds 28 tablets without desiccant. Each container is sealed with an induction seal held in place with a child resistant closure. The packaged tablets are stored at controlled room temperature 20° to 25°C (68° to 77°F). (See United States Pharmacopeia [USP].)

B4. Treatment Compliance and Adherence

Study medication will be counted to assess compliance during each scheduled clinic visit. Subjects who take ≥ 80 percent of the prescribed doses and no more than 100 percent will be considered compliant. Subjects who fall outside the boundaries of these thresholds will be counseled and re-instructed on proper dosing procedures. Medication compliance will be recorded on the CRF for each visit after reconciliation with subject-completed dosing diaries and returned used drug supply.

B5. Drug Accountability

Dosing information will be captured on a subject Dosing Diary Form. This form is part of the study source documentation and will be utilized as a source for the completion of CRFs

associated with dosing and for reconciliation of study drug administered and returned to the study site for accounting and destruction. Adequate records of study drug receipt and disposition should be maintained by pharmacy records of receipts, investigational drug orders, dispensing records, and disposition forms. The Study Monitor will also assess drug accountability and will review the pharmacy records and the Investigator study file to assure the study medication is appropriately prescribed by the Investigator or designee for the purpose of this study. At study completion, all drug supplies including partially used and empty containers must be either returned to the Sponsor or designee or destroyed per study site guidelines for destruction of investigational product immediately after drug accountability is performed by the study monitor.

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X. SAFETY MANAGEMENT

A. Clinical 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.

B. Adverse Event Reporting

All SAEs will be reported to the IRB/IEC in accordance with the IRB/IEC policies and as detailed below. AEs that are not serious will be summarized in narrative or other format and submitted to the IRB/IEC at the time of continuing review.

B1. Safety Guidance

Based on the known clinical manifestations of ALS we expect that many AEs could occur during the course of the trial that are well documented to occur during progression of the disease. These include, but are not limited to worsening neuromuscular function, depression, slurred speech, breathing difficulty, pneumonia, and death.

BioElectron Technology Corporation may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, BioElectron Technology Corporation should be provided with a copy of any post-mortem findings, including histopathology.

C. Definition of an Adverse Event

C1. Adverse Event

An **adverse event** (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The AE may be:

1. A new illness
2. Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
3. An effect of the study medication, including comparator
4. A combination of 2 or more of these factors

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term “adverse event”.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs.

Adverse events fall into the categories “non-serious” and “serious”.

C2. Definition of a Serious Adverse Event (SAE)

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

ICH guidance also recommends that important medical events that may or 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.

The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at immediate risk of death at the time of the SAE. It does not refer to a SAE which hypothetically might have caused death if it were more severe.

Clarification on the difference in meaning between “severe” and “serious”

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

[redacted] subjects who become pregnant should be immediately discontinued from the study if they have not yet received study drug. If a subject is found to be pregnant after [redacted] has received study drug, [redacted] should discontinue dosing, complete all end-of-study procedures, and be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. While pregnancy itself is not considered an AE or SAE, any pregnancy complications or an outcome other than a healthy, normal outcome will be recorded as an AE or SAE.

C3. Non-serious Adverse Event

A **non-serious adverse event** is any AE not meeting the SAE criteria.

C4. Definition of Relationship to Study Medication

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

C5. Definition of Severity

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

C6. Definition of Unexpected Adverse Event

Any AE, the specificity or severity of which is not consistent with the current investigator brochure or elsewhere in the current application, as amended, rather than from the perspective of such experience not being anticipated from the pharmacological properties of the drug.

C7. Notification of SAEs

The Investigator is responsible for promptly notifying the IRB/IEC of all study on-site SAEs, using the internal SAE reporting form, and other unanticipated problems related to research. External SAEs that are unexpected and related to the study intervention should be reported as they are received using the External SAE form (if applicable).

SAEs (whether unexpected or expected AEs) must be reported to the Sponsor (by telephone or facsimile communication) within 24 hours, followed by a completed SAE form within 2 calendar days. The designated SAE form and the instructions are provided in the Investigator's site file.

The SAE contact information will be provided separately from the protocol.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the study medication.

Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented on follow-up SAE forms.

The instructions for the completion of AE reports give more detailed guidance on the reporting of SAEs and AEs initially reported as non-serious that become serious. In the latter situation, when a non-serious event becomes serious, details must be forwarded immediately to the

Medical expert and BioElectron or BioElectron-assigned safety or pharmacovigilance staff first for assessment and then submitted to the Sponsor on the designated SAE form within 24 hours.

All relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening are to be recorded and will be reported as soon as possible to the ethics committee and BioElectron Technology Corporation will notify the FDA of fatal or life threatening SUSARs within 7 calendar days after first knowledge by BioElectron Technology Corporation that a case qualifies as an unexpected fatal or life-threatening experience, followed by a written report to the FDA within 15 days after first knowledge of the qualifying event.

Serious and unexpected AEs that are not fatal or life-threatening, but have a possible or probable relationship to the study drug must be filed with the ethics committee, and will be reported to the FDA by BioElectron Technology Corporation no later than 15 calendar days after being informed of the event.

C8. Follow-up Report

If an SAE has not resolved at the time of the initial report, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB/IEC. All SAEs should be followed until either resolved or stable.

C9. Investigator Reporting of a Serious Adverse Event to Sponsor

Reporting must be consistent with regulatory, Sponsor or general clinical research center (GCRC) requirements (if applicable).

D. Medical Emergencies

In medical emergencies, the Investigator should use medical judgment and remove the subject from the immediate hazard. The Medical Expert and the IRB/IEC must be notified regarding the type of emergency and course of action taken and the procedures for SAE reporting must be followed.

D1. Emergency Sponsor Contact

In emergency situations, the Investigator should contact the Medical Monitor: [redacted]

D2. Emergency Treatment

At present, the threshold and extent of clinical adverse effects of this study drug are not known as only limited information is available in healthy volunteers. It is anticipated in the planned study that any effects will be minimal and laboratory measurements will detect study drug effects before they become clinically significant.

XI. STUDY ADMINISTRATION

A. Treatment Assignment Methods

This is an open-label study.

B. Data Collection and Management

Monitoring and auditing procedures, developed or endorsed by BioElectron Technology Corporation will be followed in order to comply with GCP guidelines. Direct access to on-site study documentation including all source data, documentation and medical records should be ensured.

The study will be monitored by BioElectron Technology Corporation. Throughout the course of the study, the Study Monitor will make frequent contact with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the completed CRF will be compared to the source documentation for completeness, accuracy and adherence to the protocol. As part of the data audit, source documents must be made available to the Study Monitor for review. The Study Monitor will also perform drug accountability checks and will review the Investigator study file to assure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the Study Monitor will arrange for a final review of the study files, after which the files should be secured for the appropriate time period. The Investigator, or appointed delegate, will meet with the Study Monitor during the on-site visits and will cooperate in providing the documents for inspection and responding to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of BioElectron Technology Corporation or the regulatory agencies.

US and other competent regulatory authorities, the IRB/IEC, and an auditor authorized by the Sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality.

C. Data Quality Assurance

As a final step in the data management process, a 100% audit will be performed on the key safety and critical efficacy parameters. In addition, a random subject sample (10%) will be selected in order to perform a partial audit of remaining data. The purpose of this audit is to detect systematic and random errors. Any errors found from this audit will be corrected and, if the error rate is greater than 1 error per 1,000 fields (0.1%), a 100% database audit will be

performed. Systematic review of the database will be undertaken and corrections will be made to achieve an error rate of less than 0.1%.

Adverse events will be coded using MedDRA, v15.0. Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary.

D. Retention of Study Records

The following records must be retained by the Investigator for a *minimum* of 2 years after the Sponsor has notified the FDA or other competent authority that investigations have been discontinued, or after the FDA other competent authority has approved the new drug application. In accordance with European regulatory requirements (Directive 2005/28/EC and Annex 17 and 2001/83/EC and Annex1), the Sponsor may request retention for a longer period of time.

1. Signed informed consent documents for all subjects
2. Subject identification code list, screening log (if applicable), and enrollment log
3. Record of all communications between the Investigator and the IRB/IEC
4. Composition of the IRB/IEC or other applicable statement
5. Record of all communications between the Investigator and Sponsor (or Contract Research Organization [CRO])
6. List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
7. Copies of CRFs and of documentation of corrections for all subjects
8. Drug accountability records
9. Record of any body fluids or tissue samples retained
10. All other source documents (subject records, hospital records, laboratory records, etc.)
11. All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

The Investigator must obtain approval in writing from the Sponsor prior to destruction of any records.

Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, [redacted] or [redacted] must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

E. Confidentiality

Subject names will not be supplied to the Sponsor. Only the subject number and subject initials will be recorded in the CRF, and if the subject name appears on any other document (e.g., pathologist report), it must be redacted before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws.

The subjects will be told that representatives of the Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection and privacy laws, including the Health Insurance Portability and Accountability Act (HIPAA) Guidelines.

The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

F. Documentation of Study Results

A CRF will be provided for each enrolled subject.

All protocol-required information collected during the study must be entered by the Investigator, or designated representative, in the CRF. Details of CRF completion and correction will be explained to the Investigator. If the Investigator authorizes other persons to make entries in the CRF, the names, positions, signatures, and initials of these persons must be supplied to the Sponsor.

The Investigator, or designated representative, should complete the CRF pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

By signing the completed CRFs, the Investigator or Subinvestigator attests to the accuracy, completeness, legibility, and timeliness of the data collected on the CRF and casebooks.

The Sponsor will retain the originals of all CRFs. The Investigator will retain a copy of all completed CRF pages.

G. Regulatory and Ethical Considerations

G1. Risk Assessment

Based on the safety results of Study EPI589-14-01 as summarized in the Clinical Study Report, it is not foreseen that subjects will endure any risks greater than minimal at the 500 mg BID dose selected for this study.

G2. Potential Benefits of Trial Participation

This is the first study to better understand EPI-589 target engagement and potential therapeutic benefit in subjects with ALS. Therefore, we cannot assure that subjects will benefit from treatment with EPI-589. Potential treatment benefits may manifest.

G3. Risk-Benefit Assessment

The treatment options for ALS are limited, although a number of clinical interventions are being researched. Based on disease mechanism, EPI-589 mechanism of action and pre-clinical studies, EPI-589 may affect subjects with ALS. In order to further minimize risks subjects will be closely monitored with a variety of safety measures.

H. Informed Consent

Before being enrolled in the clinical study, subjects must provide written consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them. The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations and must be in a language understandable to the subject. Where required by local law, the person who informs the subject must be a physician. It should be signed and dated by all the parties concerned including the subject, legal guardian (where applicable), witness (where applicable) and the person obtaining the consent.

A copy of the signed consent document must be given to the subject. The original signed consent document will be retained by the Investigator.

The Investigator must inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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XII. PUBLICATION

A. Use of Study Results

All information concerning the product, as well as any matter concerning the operation of BioElectron Technology Corporation(such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by BioElectron Technology Corporation and are unpublished), are confidential and must remain the sole property of BioElectron. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from BioElectron Technology Corporation is obtained. The Sponsor has full ownership of the CRFs completed as part of the study.

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by BioElectron. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

If this Study is part of a multicenter clinical research study, Sponsor will act as coordinator and referee with respect to publications of the data generated thereunder. Principal Investigator shall not publish or disclose any data, result or information with respect to any matters resulting from work performed under this Protocol should this Study be conducted at other centers. Only after the completion of this Study at all centers, provision of the data to the FDA (or other agency if applicable) for review and comment, and publishing the combined data from any or all of the centers where the study is conducted, Principal Investigator may publish/present the individual results of the Study in accordance with this paragraph.

Principal Investigator may publish provided, however, that no publication, abstract, announcement or disclosure (“Publication”) shall be made until the Principal Investigator submits to Sponsor any proposed Publication for Sponsor’s review. Sponsor shall have a period of sixty (60) days to review such Publication. If Sponsor determines during the review period that the publication contains patentable subject matter, then the above sixty (60) days shall be extended to one hundred twenty (120) days in order to allow for the preparation of patent applications covering said patentable subject matter. Unless Sponsor approves in writing, no publication may contain any confidential information (other than data and results generated under the study).

Without limiting the foregoing, Institution and Principal Investigator, and all other study investigators in other study institutions, shall give due regard to Sponsor’s legitimate interests, such as manuscript authorship, coordinating and maintaining the proprietary nature of submissions to health authorities, and coordinating with other ongoing studies in the same field, and agree to accept Sponsor’s reasonable comments and suggestions with respect to such Publications.

If the Investigator is to be an author of a publication manuscript prepared by BioElectron Technology Corporation, BioElectron will allow the Investigator or CRO 60 days for full review of the manuscript before publication.

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XIII. LIST OF ABBREVIATIONS

λz	apparent terminal constant
AE	adverse event
AI	accumulation index
ALS	amyotrophic lateral sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AR	accumulation ratio
AUC	area under the curve
BID	twice daily
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
C_{max}	maximum concentration
CNS	central nervous system
CO_2	Carbon dioxide
CoQ10	Coenzyme Q 10
CRF	Case Report Form
CRO	Contract Research Organization
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTC	Common Toxicity Criteria
CTCAE	Common Toxicity Criteria for Adverse Events
CYP450	Cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
EITT	efficacy intent-to-treat
FDA	Food and Drug Administration
FEV_1	forced expiratory volume
FVC	forced vital capacity
GCP	Good Clinical Practices
GCRC	general clinical research center
GSH	glutathione
HCG	Human chorionic gonadotropin
HDPE	high density polyethylene
hERG	human ether-a-go-go related gene
HHD	handheld dynamometry
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
kg	kilogram
LFT	liver function test
MAD	multiple ascending (oral) dose
MCH	mean corpuscular hemoglobin

MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
MIP	Maximum inspiratory pressure
mL	milliliter
MPV	mean platelet volume
MRS	magnetic resonance spectroscopy
mtDNA	mitochondrial DNA
nM	nanomolar
NOAEL	no observed adverse effect level
OTC	over-the-counter
OS	oxidative stress
PK	pharmacokinetics
PO	by mouth
PT	Prothrombin Time
PTT	Partial Prothromboplastin Time
PVP	polyvinylpyrrolidone
QT	Interval between the start of the Q wave and the end of the T wave
RBC	red blood cell
RDW	red cell distribution width
ROS	reactive oxygen species
SAD	single ascending (oral)dose
SAE	serious adverse event
SOD1	superoxide dismutase soluble gene
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
T_{max}	time to peak concentration
ULN	upper limit of normal
USP	United States Pharmacopeia
VC	Vital capacity

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XIV. SIGNATURE OF SPONSOR AND INVESTIGATOR(S)

A. Declaration of Sponsor

This study protocol was subject to critical review and the information it contains is consistent with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of GCP as described in 21 CFR parts 50, 54, 56, and 312.

The Investigator will be supplied with details of any significant or new findings on EPI-589 including AEs.

Date: 17Feb2017 Signature: [redacted]

[redacted]

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