1. PROTOCOL AND PROTOCOL AMENDMENT

Document Date	Document Name
29 September 2017	EPI589-15-002 Protocol Amendment Version 5.0
29 September 2017	EPI589-15-002 Protocol Amendment SOC Version 4.0 to 5.0
17 February 2017	EPI589-15-002 Protocol Amendment Version 4.0
17 February 2017	EPI589-15-002 Protocol Amendment SOC Version 3.0 to 4.0
10 October 2016	EPI589-15-002 Protocol Amendment Version 3.0
10 October 2016	EPI589-15-002 Protocol Amendment SOC Version 2.0 to 3.0
04 January 2016	EPI589-15-002 Protocol Amendment Version 2.0
04 January 2016	EPI589-15-002 Protocol Amendment SOC Version 1.0 to 2.0
09 September 2015	EPI589-15-002 Protocol Amendment Version 1.0
09 September 2015	EPI589-15-002 Protocol Amendment SOC Version Original to 1.0
27 April 2015	EPI589-15-002 Protocol Version Original

Abbreviations: SOC, summary of changes

EPI589-15-002

A Phase 2A Safety and Biomarker Study of **EPI-589 in Mitochondrial** Subtype and Idiopathic Parkinson's Disease Subjects

Original Protocol:	27 April 2015
Protocol Amendment 1.0:	09 September 2015
Protocol Amendment 2.0:	04 January 2016
Protocol Amendment 3.0:	10 October 2016
Protocol Amendment 4.0:	17 February 2017
Protocol Amendment 5.0:	29 September 2017

BioElectron Technology Corporation
350 North Bernardo Avenue
Mountain View, CA 94043

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I. PROTOCOL SYNOPSIS

Title of study	A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects
Protocol number	EPI589-15-002
IND number	126,795
EudraCT number	2015-001786-10
Original Protocol	27 April 2015
Protocol Amendment 1.0	09 September 2015
Protocol Amendment 2.0	04 January 2016
Protocol Amendment 3.0	10 October 2016
Protocol Amendment 4.0	17 February 2017
Protocol Amendment 5.0	29 September 2017
Investigative Drug	EPI-589
Study Sponsor	BioElectron Technology Corporation 350 North Bernardo Avenue Mountain View, CA 94043
Investigators and Investigative Sites	• [redacted] USA • [redacted] USA • [redacted] UK • [redacted] USA • [redacted] Germany
Study population	Approximately 40 subjects with Parkinson's disease (PD) including 20 subjects with genetically-defined subtypes

Rationale for Study

Mitochondrial pathophysiology

It is now well appreciated that defects in mitochondrial function contribute to the pathophysiology of PD both in subjects with defined genetic defects as well as those with idiopathic forms of the disease.

High morbidity

Despite the available therapies for symptomatic relief, PD remains a highly morbid disease. There are no approved treatments for PD capable of modifying disease progression.

Pre-clinical efficacy data

EPI-589 is a redox active molecule that has demonstrated potency (EC50 < 100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with idiopathic and familial PD subtypes including PINK1, parkin and LRRK2.

Study objectives

Primary Objective

To evaluate the effects of EPI-589 on safety as assessed by occurrence of drug-related serious adverse events in subjects with PD.

Secondary Objectives

To evaluate the effects of EPI-589 in subjects with PD on:

1. Fasting glutathione cycle biomarkers as measured in blood, cerebral spinal fluid, and urine
2. Clinical disease state as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D
4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA) and
5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery and Asberg Depression rating scale (MADRS)
6. Pharmacokinetics
7. Hematology, blood chemistry, electrocardiogram

Study design	Open-label study with 30-day run-in phase.
Planned number of subjects	Approximately 40 subjects (20 with genetically-defined subtypes of PD and 20 idiopathic PD subjects). (Adaptive design component allows enrollment of up to 20 additional subjects with idiopathic PD to try to achieve a total of 20 subjects that have a biomarker response to EPI-589.)
Study duration	3 months (85 days ± 3 days) of study treatment preceded by a 1-month baseline parameter run-in period.
Test product, mode of administration, and dose	Test product EPI-589 in a tablet formulation at a strength of 250 mg Mode of Administration Oral with meal Dose EPI-589 500-mg BID (morning and evening dose along with food)
Reference therapy, dose, and mode of administration	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 (all subjects)	1. Hoehn and Yahr stage ≤ 3.0 2. Ambulatory with or without assistance 3. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., hormonal methods, including oral, subcutaneous, and intrauterine; barrier methods, including [redacted] condom, [redacted] condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study treatment. 4. Willingness and ability to comply with study procedures 5. If on medications for PD drugs, then medication regimen must be stable for 60 days prior to enrollment 6. Abstention from use of other investigative or non-approved drugs for the duration of the trial *For Idiopathic Subjects* 7. A diagnosis of idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit 8. Age 40 to 75 years 9. Within 5 years of diagnosis of Parkinson's disease *For Genetic Subtype Subjects* 10. A confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LRRK2 or other mitochondrial genetic subtype 11. Age 21 to 75 years
Exclusion criteria	1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation 2. Use of antioxidant supplements, specifically vitamins E and C beyond the recommended daily allowance 3. Other Parkinsonian disorders 4. MoCA score of <24 5. Revised Hamilton Rating Scale for Depression ≥ 11 6. Parkinsonism due to drugs or toxins 7. Diagnosis of any other clinically significant neurologic disease that will

	confound the assessment of effect of study drug on disease progression 8. Malignancy within past two years 9. Pregnant or plans to become pregnant or breast feeding 10. History of stroke 11. History of brain surgery 12. Hepatic insufficiency with liver function tests (LFTs) > 3 times upper limit of normal 13. Renal insufficiency as defined by creatinine > 1.5 times normal 14. End stage cardiac failure 15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD
Treatment	Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues. Post-treatment follow-up will be at least 10 days and up to 30 days after last dose.
Efficacy variables	1. Fasting blood-based glutathione biomarkers 2. Fasting CNS biomarkers 3. Fasting urine-based biomarkers 4. MDS-UPDRS 5. Non-motor Symptoms Scale (NMSS) 6. PDQ-39 7. EQ-5D 8. MoCA 9. Beck Depression Inventory (BDI) 10. Montgomery & Asberg Depression rating scale (MADRS) 11. Timed motor tests in ON state only (for subjects on dopamine therapy) 12. Pharmacokinetics

Safety variables	Clinical 1. Routine assessments of AEs and SAEs 2. Dose limiting toxicities 3. Electrocardiogram 4. C-SSRS 5. Routine serum chemistries with liver function tests 6. Routine hematology tests with coagulation tests
Statistical Considerations	Data Analysis This is a within-subject, controlled open-label study seeking to determine the safety and tolerability of EPI-589 in patients with PD as well as to determine if EPI-589 can alter the biochemical signature of PD as assessed by peripheral blood biomarkers, CNS biomarkers, brain imaging biomarkers, and urine biomarker analysis. In addition, data on a number of disease-relevant clinical measures will be collected.

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II. SCHEDULE OF ASSESSMENTS AND DOSING SCHEDULE

Tests	-2 to -1 Months		DayO		Month 1	Month 2	Month3 End of Treatment Visit	Post-Treatment Follow-up
	Screening	Run-in (upto 30 days from screenin2)	Baseline (27-33 days from run-in		Day29 (±3 days)	Day 57d (± 3 days)	Day85 (±3 days)	Up to 30Days afte1·Last Dose
Informed consent				Day 1 First Dosei				
Inclusion/Exclusion criteria								
Past Medical history								
Pre:wous genetic testing review								
Physical examh & Vital signs	h							
Heightg & weight	g		-					
12-lead ECG			-					
Hematology (including coagulation panel)			a,f		f		f	
Semm Chemistiy			a,f		f		f	
Pregnancy test"								
C-SSRS								
Monti·eal Cognitive Assessment								
DaTscan (for idiopathic subjects)								
Revised Hamilton Rating Scale for Depression								
Subject enrolls in study		X						
Fasting blood-based glutathione cycle biomarkers								
Fasting Lumbar puncture (CNS biomarkers)								
Fasting Urine-based biomarkers								
MDS-UPDRS								
Timed motor tests (for subjects on dopaniine therapy)								
NMSS, PDQ-39, EQ-5D								
BDI,MADRS								
Dmg plasma concenti·ation°					c		c	
AE/SAE assessment	•	•	•			d	d	-
Concomitant medications assessment						d	d	-
Post-Treatment Assessments•								•

a. Screening values can be used if done w-ithin one month of baseline and if completed under fasted conditions

• Female subjects of childbea1mg potential must have a negative pregnancy test.

c. Full plasma concenti·ation profile w-ill be obtained at Time= 0, and 0.5, I, 2, 4, 6, 8, and12 hours after dosing from the first 10 subjects to complete I month of therapy at each site.12 hour PK can be obtained at time 0.

d. Month 2 assessments can be done by telephone. Any new AEs and associated concomitant medications reported at Month 3 must be followed for 30 days; this follow up may be conducted by telephone.

e. AE/SAE and concomitant medication assessments conducted bytelephone for at least 10 days after last dose and if there are any ongoing or new AEs noted at month 3, then the follow up will be up to 30 days after last dose. Additional assessments detemiined at Investigator discretion. SAEs are tracked from the time ICF is signed and all other AEs are tracked from the time first dose is administered;
f. TI1e baseline and all subsequent laboratory assessments should be obtained under fasting conditions.
g. Height is measured at screening visit only.
h. The findings from breast exam will be captured as pa1t of the screening physical exam. The findings from breast exams conducted within 6 months of the screening visit and those collected as pa1t of medical history, may be used for the screening physical exam.
1. First dose may be taken same day as baseline visit after all baseline assessments are completed

A. Schedule of Dosing

	-2 to -1 Months		Day0		Month 1	Month2	Month3	Post-Treatment
Dosing Schedule	**Screening**	**Run-in (±30 days)**	**Baseline**		**Day29 (±3 days)**	**Day** 57d **(±3 days)**	**Day85 (±3 days)**	**Up to30 Days after Last Dose•**
EPI-589 500-mg BID (hvice daily with food)								
Dispense Study Drug								
Dmg Reconciliation with diaries								

III. INTRODUCTION

A. Background Information and Rationale

Parkinson's disease (PD) is a highly morbid neurodegenerative movement disorder that has a number of neuromuscular, cognitive and neuropsychiatric manifestations as well as non-neurological symptoms. PD is the second most common neurodegenerative disorder with an estimated prevalence of 6.3 million people worldwide (EPDA).

PD has long been considered a non-genetic (idiopathic) disease; however, about 5% of patients have an identifiable mutation. Disease onset typically occurs after age 50, however, in a subset of patients, disease onset can occur at a younger age. The primary motor symptoms result from death of dopamine-producing cells in the pars compacta region of the substantia nigra. However, the mechanisms underlying this cell death and disease pathology remain poorly understood. There is no approved treatment for PD capable of modifying disease progression. Current therapies partially address disease motor symptoms through levodopa or dopamine agonists or other agents, and other disease symptoms (e.g. neuropsychiatric symptoms), but disability tends to increase over time despite these treatments.

The association of PD with mitochondrial pathology and high levels of oxidative stress are well established. Increased levels of oxidative stress have been consistently measured in post-mortem specimens from PD patients (Maarouf 2012, Reale 2012). The occurrence of PD-like symptoms in heroin addicts exposed to MPTP in the 1980s established a first link between PD and mitochondrial injury (Langston 1983, Dauer and Przedborski 2003). MPTP inhibits complex 1 of the mitochondrial respiratory chain and induces degeneration of dopaminergic cells through oxidative stress-mediated injury. The link between mitochondrial injury and PD was further strengthened by the induction of PD symptoms following exposure to another neurotoxic complex 1 inhibitor, rotenone (Betarbet et al 2000, Greenamyre et al. 2003), which like MPTP has come to be used in pre-clinical testing for its phenotypic similarities to PD.

Furthermore, the identification of genetic mutations such as PINK1, parkin, LRRK2 and others in mitochondrial genes in familial PD patients provided the strongest link between the mitochondria and PD (Winklhofer and Haass 2010). Normally these genes influence oxidative balance and provide neural protection of the dopaminergic neurons that are affected by PD. PINK1 and parkin are involved in protecting against oxidative stress (OS) and overabundant reactive oxygen species (ROS), and are implicated in cell morphology and dynamics, as well as in the preferential degradation of dysfunctional mitochondria or "mitophagy" (Ashrafi et al. 2014). Mutant LRRK2 leads to the accumulation of misfolding intracellular protein accumulations, cell stress and apoptosis (Giasson et al. 2006, Zhu et al. 2006).

The importance of oxidative stress in PD pathology is further substantiated by the measurement of decreased levels of reduced glutathione in the brains of patients with PD (Holmay et al. 2013). Glutathione levels are low at very early stages of PD and correlate with disease severity (Riederer et al. 1989), and experimental induction of glutathione depletion leads to mitochondrial complex I dysfunction (Jha et al, 2000;). Reduced glutathione is an essential intermediary

metabolite that serves as the primary native cellular antioxidant. In a state of high oxidative stress, elevated levels of ROS outstrip the supply of glutathione (GSH) resulting in depletion of GSH and ROS-mediated cell death.

Given the important role of oxidative stress and mitochondrial pathology in PD, a redox-active therapy that could target key pathways in cellular OS response pathways may hold promise for the treatment of PD.

B. Rationale for the Study of EPI-589 in Parkinson's Disease

EPI-589 is a redox active molecule that has demonstrated potency (EC50 <100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with idiopathic and familial PD genetic subtypes including PINK1, parkin and LRRK2.

In these cell-based assays, primary fibroblasts from patients (and control) were pre-incubated with and without test compound, then treated with L-buthionine-(S,R)-sulfoximine (BSO), a GSH synthesis inhibitor, to initiate depletion of cellular GSH. GSH depletion has been shown to lead to OS and disruption of calcium homeostasis resulting in loss of the mitochondrial membrane potential and cell death. Under these conditions, the control cells are resistant to the stress and the fibroblast cells from patients with disease indications die within 36 to 48 hours. Pretreatment of cells with EPI-589 prior to initiation of GSH depletion potently protected against oxidative stress-mediated cell death, with EC_{50} response concentrations of 16 to 52 nM. (Table 1).

Table 1: Cell Line Rescue with EPI-589 in Parkinson's Disease Genetic Subtypes

	EPI-589 EC_{50} (nM range)
PINK1	26-36
LRRK2	16-18
parkin	42-52

C. Name and Description of Investigational Product

The IUPAC name of 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 derived from resolved (R)-Trolox®, a derivative of vitamin E in the form of a pale yellow to yellow solid. The EPI-589 drug product will be provided in a 250-mg tablet formulation.

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. In 28-day, 91-day, 6-month, and 9-month repeat-dose toxicity studies in rat and cynomolgus monkey, the no observed adverse effect level (NOAEL) was 300 mg/kg/day, corresponding to terminal combined mean C_{max} values of 37,717 to 56,500 ng/mL (rat) and 14,300 to 24,500 ng/mL (monkey), and terminal combined mean area under the plasma concentration-time curve (AUC) values of 149,495 to 297,000 ng.h/mL (rat) and 47,300 to 124,000 ng.h/mL (monkey) (Studies 1660-038, 1660-039, 1660-063, 1660-064, 1660-079, and 1660-080).

The dose-limiting drug-associated toxicity observed in the 28-day, 3-month, and 9-month (monkey) animal studies was hemolysis in rat and significant acute toxicity leading to moribundity with indication of skeletal, renal, liver, and lymphoid tissue effects in monkey. All clinical program investigators have been required to monitor hematology parameters and clinical chemistry parameters for kidney, liver, and muscle function in all EPI-589 subjects. To date, no dose-limiting toxicities have been reported with EPI-589 in humans.

A phase 1 clinical study demonstrated that healthy young and elderly subjects administered 500 mg EPI-589 BID for 14 days showed mean C_{max} values of 1,890 to 1,960 ng/mL and mean AUC values of 10,480 to 11,000 ng.h/mL (Study EPI589-14-01). These plasma concentrations are well below the 300 mg/kg/day NOAEL exposure values in monkey, the most sensitive toxicity species, corresponding to repeat-dose exposure safety margins of approximately 7- to 12- fold for the mean C_{max} and 4- to 8-fold for the mean AUC.

During the 9-month repeat-dose toxicity study in monkey, animals were administered 60, 100, 300, or 500 mg/kg/day EPI-589 PO (Study 1660-080). The NOAEL was 300 mg/kg/day. Monkeys that received 500 mg/kg/day showed significant test-article related moribundity after receiving only three or four doses resulting in three animals being euthanized on Days 4, 5, and 7 and the remaining animals being euthanized on Day 11. Animals exhibited significant elevations in AST and ALT values, and microscopic findings in multiple sites in the skeletal muscle, kidney, liver, and lymphoid tissues. The primary cause of morbidity in the three animals euthanized on Days 4, 5, and 7 was myofiber degeneration and degenerative changes in kidney (3/3 animals). The toxicity observed following administration of three to four doses of 500 mg/kg/day EPI-589 were similar and consistent with toxicity observed following administration of two doses of 1,000 mg/kg/day during the 28-day toxicity study (Study 1660-038), likely due to similar exposures between the two doses. The margin of exposure between healthy young and elderly humans exposed to 500 mg BID EPI-589 (relevant clinical dose) for 14 days (Study EPI589-14-01) and monkeys exposed to EPI-589 PO on Day 1 is approximately 26-fold for the mean C_{max} and 21-fold for the mean AUC_{last} at 500 mg/kg, and approximately 29-fold for the mean C_{max} and 27-fold for the mean AUC_{last} at 1,000 mg/kg.

During the 6-month repeat-dose toxicity study in rat, animals were exposed to up to 300 mg/kg/day EPI-589 PO (Study 1660-079). The NOAEL was 300 mg/kg/day. Rats exposed to 300 mg/kg/day exhibited mild test-article related effects on hematology parameters consistent with hemolysis and compensating reticulocytosis. These findings were not considered adverse.

During the 91-day repeat-dose toxicity studies, rat and monkey were exposed to up to 300 mg/kg/day EPI-589 PO (Studies 1660-063 and 1660-064). The NOAEL for the rat study was 300 mg/kg/day and the no observed effect level (NOEL) for the monkey study was 300 mg/kg/day. Male rats exposed to 300 mg/kg/day and female rats exposed to ≥ 100 mg/kg/day exhibited mild test-article related effects on hematology parameters consistent with hemolysis and bone marrow regeneration. These findings were not considered adverse.

During the 28-day repeat-dose toxicity studies, rat and monkey were exposed to up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-039 and 1660-038). The NOAEL for both studies was 300 mg/kg/day. Rats exposed to 1,000 mg/kg/day exhibited adverse 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 showing corresponding microscopic pathology. The majority of these findings were resolved following the 28-day recovery period. Monkeys exposed to 1,000 mg/kg/day showed significant test-article related moribundity after receiving only two doses resulting in half the animals in the high dose group being euthanized on Days 3 and 4 and the remaining animals being euthanized on Day 9. Animals exhibited significant elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values, and microscopic findings in multiple sites in the skeletal muscle, kidney, liver, lymphoid tissues, and heart. The primary cause of morbidity in five animals euthanized on Days 3 and 4 was renal tubular degeneration and necrosis (2/5 animals) or was not able to be determined (3/5 animals).

Development and reproductive toxicology studies were conducted in rat and rabbit at doses up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-069, 1660-067, and 1660-068). The NOAEL for reproductive toxicity in rat was demonstrated to be 1,000 mg/kg/day (Study 1660-069). The NOAEL for developmental toxicity in rat and rabbit during the embryofetal studies was deemed to be 300 mg/kg/day (Studies 1660-067 and 1660-068).

Rats exposed to 1,000 mg/kg/day exhibited 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. Rabbits exposed to 1,000 mg/kg/day exhibited 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 young and elderly humans exposed to 500 mg BID EPI-589 (relevant clinical dose) for 14 days (Study EPI589-14-01) and rabbits exposed to 300 or 1,000 mg/kg/day EPI-589 is approximately 22-fold and 84-fold, respectively. 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 (Study AD58AS.502ICH.BTL); 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 (Study AD58AS.331ICH.BTL); and negative in the in vivo micronucleus assay in rat (Study AD58AS.125012ICH.BTL). These data indicate a low clinical mutagenicity risk.

In secondary pharmacodynamics in vitro receptor/ion channel binding studies, EPI-589 did not significantly affect off-target molecular targets (Study EPI-BA-186). In safety pharmacology studies, EPI-589 did not significantly affect ion channel current in the human ether-a-go-go-related gene (hERG) assay (Study 130719.FEK); did not adversely affect electrocardiogram (ECG) parameters during the 28-day, 3-month, or 39-week repeat-dose toxicology studies in monkey at doses up to 1,000 mg/kg/day (only Day 1 data collected for animals administered 500 or 1,000 mg/kg/day and up to Day 91 data collected for animals administered up to 300 mg/kg/day) (Studies 1660-038, 1660-064, and 1660-080); and did not change respiratory function or adversely impact neurobehavioral function in rat at doses up to 1,000 mg/kg (Studies 1660-051, 1660-050, and 1660-063).

EPI-589 is approximately 60% protein bound in human plasma (Study MC14M-0067). EPI-589 did not significantly induce cytochrome P450 (CYP) enzymes (Study MC12M-0037) and exhibited weak direct inhibition of CYP2B6, CYP2C8, CYP2C9, and CYP3A4/5 (both midazolam and testosterone as probe substrates) with estimated IC_{50} (μM) values and R values based on free plasma concentrations (shown in parentheses) of 28 (1.25), 40 (1.18), 92 (1.08), 34 (1.21), and 53 (1.13), respectively (Study MC14M-0020). EPI-589 is metabolized by reductases in the liver cytosol and microsomal subcellular fractions, and to a lesser extent by the family of CYP enzymes (Study MC14M-0018). EPI-589 is an inhibitor of the BCRP efflux transporter, possibly an inhibitor of the MATE1, OATP1B3, MATE2-K, OCT1, OATP1B1, OCT2 and OAT3 uptake transporters (in order of increasing inhibitory potential), and possibly a substrate of the MDR1 and BCRP efflux transporters (Edison-04-25Feb2014).

An in vivo primary pharmacodynamic study demonstrated that EPI-589 significantly reduced disease progression as measured by standard functional outcomes of rotarod test and forelimb deformity score as compared with vehicle controls in the gold standard in vivo wobbler mouse model of ALS. These EPI-589 effects were superior to riluzole. In addition, EPI-589 had synergistic effects with riluzole when co-administered. These results indicate that EPI-589, alone or in combination with riluzole, may have beneficial effects on the progression of neuromuscular dysfunction in ALS patients (Study R-PH-EPI-589-002).

In vitro primary pharmacodynamics studies demonstrated EPI-589 is a potent rescue agent in cellular models of diseases of energy metabolism and oxidative stress. In vitro cellular models utilizing primary human fibroblasts from patients with ALS, Parkinson's disease and other diseases characterized by high levels of oxidative stress, or striatal cells derived from mouse models of Huntingdon's disease were used to assess the potential of EPI-589 to mitigate the harmful effects of oxidative stress (Studies EPI-BA-000216, EPI-BA-000363, and EPI-BA-000362). Pretreatment of patient cells with EPI-589 potently protected against oxidative stress-mediated cell death in a concentration dependent manner. Furthermore, EPI-589 normalized 3-nitrosotyrosine (3NT) levels, a biomarker of oxidative stress, and increased glutathione levels in mouse striatal cells under oxidative stress conditions.

The nonclinical laboratory studies conducted in accordance with the United States Food and Drug Administration (FDA) Good Laboratory Practice (GLP) Regulations 21 Code of Federal Regulations (CFR) Part 58 were conducted in conformance with the principles of OECD-GLP in the United States, a country that is part of the OECD Mutual Acceptance of Data process.

D2. Clinical Studies

Phase I Study EPI589-13-022 evaluated the pharmacokinetics, safety and tolerability of single ascending oral doses (SADs) of EPI-589 in healthy subjects and a preliminary evaluation of safety and tolerability data was performed. Sixteen AEs were reported in the 36 subjects who received administration of EPI-589. Ten subjects (27.8%) who received EPI-589 (and 2 subjects, 20% on placebo) reported AEs that were assessed as related. All were mild and resolved during the study, with the exception of a common cold (1 subject) and cold sore (1 subject). 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. Twenty-six subjects (65.0%) on EPI-589, and 8 subjects (80%) on placebo reported AEs. Twenty-four of 34 AEs were considered by the Investigator to be related to EPI-589. Nineteen subjects (47.5%) on EPI-589, and 6 subjects (60%) on placebo reported AEs that were assessed as related. All adverse events were mild, except for 1 AE which was moderate (unrelated brain contusion). All AEs were resolved during the study, with the exception of one, which was a common cold. 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 the MAD study it may be concluded that there is no objection to proceed with treatment with 250-mg, or 500-mg doses of EPI-589.

E. Human Pharmacokinetics

EPI-589 was fast absorbed following oral administration in SAD Study EPI589-13-022. The median C_{max} was attained approximately within 1 hour under fasted conditions after dosing. The median T_{max} values were attained in 0.50 to 1.00 hours over the dose range of 50 to 1000 mg under fasted conditions and 3.01 hours at the 500 mg dose level under fed conditions. Mean half-life ranged from 5.55 to 10.7 hours over the dose range of 50 to 1000 mg under fasted conditions and 4.91 hours at the 500 mg dose level under fed conditions. Half-life was independent of the dose levels over the dose range of 50 to 1000 mg under fasted conditions. The rate of EPI-589 absorption, as measured by C_{max}, was decreased by 24.07% under fed conditions at the 500 mg dose level. The extent of absorption as measured by AUCs (AUC_{0-t} or AUC_{0-inf}) was not affected under fed conditions in the 500 mg dose groups.

In MAD study EPI589-14-01, 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 of various ages and smoking status. No significant effects of age or smoking on EPI-589 pharmacokinetics were observed in this study. Dose proportionality existed in the exposures (AUC_{0-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

EPI589-15-002: A Phase 2A Safety and Biomarker Study of EPI-589 in in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects.

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 morning and evening with meals.

H. Compliance Statement

This study will be conducted in full accordance with all applicable research policies and procedures, the EU Clinical Trials Directive, all applicable EU and 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, will obtain consent and will 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.

I. 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 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 PD.

B. Secondary Objectives

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

1. Fasting glutathione cycle biomarkers as measured in blood, cerebral spinal fluid, and urine
2. Clinical disease state as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D
4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA)
5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery & Asberg Depression rating scale (MADRS)
6. Pharmacokinetics
7. Hematology, blood chemistry, electrocardiogram

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V. INVESTIGATIONAL PLAN

A. General Schema of Study Design

Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues.

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects. Given that the investigational drug targets an enzyme key to glutathione synthesis and that glutathione depletion has been found to be associated with PD, we are seeking to determine the safety and potential biochemical benefit of EPI-589 in PD subjects as assessed by glutathione cycle biomarkers. If we determine that there are a subset of idiopathic PD patients—whether due to disease stage or baseline biomarker profile—who are more likely to be EPI-589 responsive, we will seek to enroll additional numbers of these subjects in the adaptive phase so that we can increase the number of likely biomarker responsive subjects. EPI-589 will be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues.

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 run-in scans, CNS, blood-based biomarker, urine-based biomarker and clinical measurements will be collected.

A3. Baseline

Baseline assessments, scans, blood-based biomarker, urine biomarker, 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 (morning and evening dose along with food).

Blood-based biomarker, urine biomarker, and clinical measurements will be collected at Day 29 (± 3 days) and Day 85 (± 3 days).

A5. End of Treatment

End of treatment data will be collected at the last study visit Day 85 (± 3 days).

AEs reported as ongoing at Day 85 (± 3 days) and/or any concomitant medications associated with such events 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.

A6. Post-Treatment Follow-up

Post-Treatment Follow-up will be at least 10 days after last dose and if there are any ongoing or new AEs noted at month 3, then the follow up will be up to 30 days after last dose. AE/SAE and concomitant medication assessments conducted by telephone. Additional assessments to be determined at Investigator discretion.

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 biomarker and clinical baseline measurements. EPI-589 will then be administered for 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues. A post-treatment follow-up will be conducted at least 10 days and up to 30 days after last dose.

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

This study will be conducted at five study sites:

- [redacted] UK
- [redacted] USA.
- [redacted] Germany
- [redacted] USA
- [redacted] USA

Approximately 40 subjects with PD are projected:

- 20 with genetically-defined subtypes
- 20 PD idiopathic PD

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects to achieve a higher number of subjects in

whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the same study protocol and outcome metrics.

D. Study Population

D1. Inclusion Criteria

1. Hoehn and Yahr stage ≤ 3.0
2. Ambulatory with or without assistance
3. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., hormonal methods, including oral, subcutaneous, and intrauterine; barrier methods, including [redacted] condom, [redacted] condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study treatment.
4. Willingness and ability to comply with study procedures
5. If on medications for PD drugs, then medication regimen must be stable for 60 days prior to enrollment
6. Abstention from use of other investigative or non-approved drugs for the duration of the trial

For Idiopathic Subjects

7. A diagnosis of idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit
8. Age 40 to 75 years
9. Within 5 years of diagnosis of Parkinson's disease

For Genetic Subtype Subjects

10. A confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LRKK2 or other mitochondrial genetic subtype
11. Age 21 to 75 years

D2. Exclusion Criteria

1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation
2. Use of antioxidant supplements, specifically vitamins E and C beyond the recommended daily allowance
3. Other Parkinsonian disorders
4. MoCA score of <24
5. Revised Hamilton Rating Scale for Depression ≥ 11
6. Parkinsonism due to drugs or toxins
7. Diagnosis of any other clinically significant neurologic disease that will confound the assessment of effect of study drug on disease progression
8. Malignancy within past two years
9. Pregnant or plans to become pregnant or breast feeding

10. History of stroke
11. History of brain surgery
12. Hepatic insufficiency with liver function tests (LFTs) > 3 times upper limit of normal
13. Renal insufficiency as defined by creatinine > 1.5 times normal
14. End stage cardiac failure
15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD

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VI. STUDY PROCEDURES

A. Screening Visit

Screening evaluations will be performed within two months of first dose. The Investigator will inform each prospective subject of the nature of the study, explain the potential risks, and must 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. Receipt and review of previous testing including genetic tests
4. Physical examination* including vital signs
5. Height** and weight
6. 12-lead ECG
7. Laboratory assessments for hematology, coagulation, and serum chemistry*** (See Sections VII.D2.a and VII.D2.b)
8. Urine pregnancy test (women of childbearing potential must have a negative urine pregnancy test; see Section VII.D2.c)
9. MDS-UPDRS
10. MoCA
11. DaTscan (for idiopathic subjects only)
12. Revised Hamilton Rating Scale for Depression
13. SAE assessments
14. Concomitant medications assessment (last 60 days prior to enrollment)

*Breast exam is at screening physical exam only.
** Height is measured at screening visit only.
***Screening values can be used if done within one month of baseline and if completed under fasted conditions

A1. Run-in Assessments

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 within one month for Run-in assessments. These will 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. Fasting blood-based glutathione cycle biomarkers
2. Fasting CNS biomarkers (lumbar puncture)
3. Fasting urine biomarkers
4. Timed motor tests (for subjects on dopamine therapy)
5. AE/SAE assessments
6. Concomitant medications review

B. Treatment Phase

After the Run-in phase, the subject must return to the clinic within 30 days (± 3 days) for baseline assessments. In-clinic study visits are scheduled at Month 1 and Month 3. The Month 2 study assessments can be conducted via telephone. End of treatment assessments will be conducted at the Month 3 study visit. Pharmacokinetic sampling takes place at Month 1 and Month 3. The baseline and all subsequent laboratory assessments should be obtained under fasting conditions.

B1. Baseline Assessments

The following will be assessed or performed at this visit.

1. Physical examination including vital signs
2. Height and weight*
3. 12-Lead ECG*
4. Fasting blood-based GSH cycle biomarkers
5. Fasting urine-based biomarkers
6. Laboratory assessments for hematology, coagulation and serum chemistry*
7. Urine pregnancy test (females of child bearing potential)
8. C-SSRS (Columbia Suicide Severity Rating Scale)
9. MDS-UPDRS
10. NMSS, PDQ-39, EQ-5D
11. BDI, MADRS
12. Timed motor tests (for subjects on dopamine therapy)
13. AE/SAE assessments
14. Concomitant medications review

* Screening results for these assessments may be used if obtained within 1 month of Baseline and if they are completed under fasted conditions. The baseline laboratory assessments should be obtained under fasting conditions.

B2. Study Visit Assessments

- Month 1 Clinic Visit (Day 29 ± 3 days):

The following will be assessed or performed at the Month 1 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry*
5. Urine pregnancy test (females of child bearing potential)
6. C-SSRS
7. Fasting blood-based GSH cycle biomarkers
8. Fasting urine-based biomarkers
9. MDS-UPDRS

10. Pharmacokinetics**: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.12 hour time point may be obtained at 0 hour.
11. AE/SAE assessments
12. Concomitant medications review

* The laboratory assessments should be obtained under fasting conditions.

- Month 2 Visit (Day 57 ± 3 days)

Month 2 assessments can be conducted by telephone and must include review of:

1. AE/SAE assessments
2. Concomitant medication

- Month 3 Clinic Visit (Day 85 ± 3 days)

The following will be assessed or performed at the Month 3 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry*
5. Urine pregnancy test (females of child bearing potential)
6. C-SSRS
7. Fasting blood-based GSH cycle biomarkers
8. Fasting urine-based biomarkers
9. Fasting CNS biomarkers
10. MDS-UPDRS
13. Pharmacokinetics**: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing. 12 hour time point may be obtained at 0 hour.
11. AE/SAE assessments
12. Concomitant medications review
13. MoCA
14. NMSS, PDQ-39, EQ-5D
15. BDI, MADRS
16. Timed motor tests (for subjects on dopamine therapy)

* The laboratory assessments should be obtained under fasting conditions.

*B3. Pharmacokinetics***

Plasma concentration samples will be collected from 20 subjects (10 idiopathic and 10 with genetically defined subtypes) at the following time points:

- Month 1 (Day 29 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose
- Month 3 (Day 85 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose

** 12 hour PK can be obtained at time 0

The pharmacokinetics samples collection will be monitored as subjects are enrolling and sponsor will alert each principal investigator once the required samples for each subtype are obtained.

B4. Early Termination Study Visit

Subjects who terminate from the study after receiving first dose and prior to the completion of all scheduled visits should have the end of treatment visit assessments completed as soon as possible.

C. End of Treatment Visit

End of treatment visit takes place at Month 3 (Day 85 ± 3 days) and includes the assessments listed in Section VB2 Study Visit Assessments.

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. Post-Treatment Follow-up

Post-Treatment Follow-up will be at least 10 days and up to 30 days after last dose, with AE/SAE and concomitant medication assessments conducted by telephone. Additional assessments to be determined at Investigator discretion.

E. Unscheduled Visits

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

F. Concomitant Medication

Any medication taken by a subject ≤ 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 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 consulting the Investigator.

G. 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. However if the subjects are on high doses of Vitamin E and C and are eligible to participate , they are allowed a 2 weeks washout period prior to enrollment
2. Participation 3 months prior to and for the duration of the study in a trial of a device, drug or other therapy for PD

H. Subject Withdrawals

Subjects receive study treatment until treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The following conditions require subject discontinuation from all study treatment:

1. At their own request or at the request of their legally authorized representative
2. If a subject experiences an adverse event that is deemed related to treatment with EPI-589 and in the Investigator's or the Sponsor's medical judgment continuation of treatment would be detrimental to the subject.
3. At the specific request of a regulatory agency for termination of treatment of an individual subject or all subjects under the protocol
4. Subject participation in another clinical study using an investigational agent or investigational medical device
5. Use of prohibited medications such as vitamins E and C beyond the recommended daily allowance.
6. Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use medically accepted methods of contraception
7. If a subject becomes pregnant.
8. Significant noncompliance with the protocol in the opinion of the Investigator or the Sponsor

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 should 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 PD.

B. Secondary Endpoints (Efficacy)

1. Fasting blood-based biomarkers
2. Fasting CNS-based biomarkers
3. Fasting urine-based biomarkers
4. MDS-UPDRS
5. NMSS
6. PDQ-39
7. EQ-5D
8. MoCA
9. BDI
10. MADRS
11. Timed motor tests as ON state only (for subjects on dopamine therapy)
12. Pharmacokinetics

C. Secondary Endpoints (Safety)

1. Routine assessments of AEs and SAEs
2. Dose limiting toxicities
3. Routine serum chemistries with liver function tests
4. C-SSRS
5. Routine hematology tests with coagulation tests
6. Electrocardiogram

D. Screening and Baseline Evaluation

D1. Physical Examination, height and weight

Complete physical exams will be conducted (excluding genital/rectal exam) at protocol specified study visits. 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, heart, abdomen, and extremities.

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).

The findings from breast exam will be captured as part of the screening physical exam. The findings from breast exams conducted within 6 months of the screening visit and those collected as part of medical history, may be used for the screening physical exam.

Medical history and demographics including age, gender, race, will be collected at screening visit. Weight (kg) will be measured in ordinary indoor clothing (i.e., street clothes, scrubs, etc.) with shoes off. Height will be recorded in centimeters (cm) and need not be repeated after screening visit.

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.

D2. Laboratory Evaluations

Subjects 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 I).

a. Hematology

   a. Erythrocytes: red blood cell (RBC) count, hematocrit, hemoglobin, mean corpuscular volume (MCV)
   b. Leukocytes: white blood cell count (WBC) and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils).The differential can be recorded as an absolute value or percentages.
   c. Platelets: platelet count
   d. Coagulation: prothrombin time (PT) with INR, and partial thromboplastin time (PTT)

b. Serum chemistry

   a. Liver: Alkaline Phosphatase (ALP), ALT (serum glutamic-pyruvic transaminase [SGPT]), AST (serum glutamic-oxaloacetic transaminase [SGOT]), bilirubin (total and direct), gamma-glutamyl transferase (GGT), and lactic dehydrogenase (LDH)
   b. Renal: blood urea nitrogen (BUN), and creatinine
   c. Electrolytes: sodium, potassium, chloride and bicarbonate
   d. General: creatine phosphokinase (CPK), total protein, albumin, calcium, magnesium, glucose, phosphate
   e. Lipids: cholesterol (total), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL), cholesterol, and triglycerides

c. Urine pregnancy test

1. Human chorionic gonadotropin (HCG) beta subunit will be measured on all female subjects of childbearing potential.

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.

Diagnoses associated with any NIH Common Terminology Criteria for Adverse Events (CTC v4.03) Grade 3 or 4 laboratory abnormalities will be recorded as adverse events (AEs**)** on the CRF. The recorded event 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.

D3. Dose Limiting Toxicity (DLT)

There were no DLTs noted in the phase 1 study; the dose-limiting (NOAEL) in nonclinical studies, as described in the protocol were increased LFTs (ALT, AST), rhabdomyolysis (elevated CPK), renal dysfunction (likely secondary to rhabdo), and marrow toxicity (most notably hemolysis). Therefore for this study, any increased LFT, BUN/Cr or CPK (or CK) should be considered related to study drug and should be designated as a DLT. If there is a DLT, a dose reduction will be attempted. Contact the medical monitor for further instructions.

D4. 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.

E. Sample Collection Procedures, Bioanalytical Methods and Sample Shipment

Subject samples will be identified by unique sample codes.

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

F. Efficacy Evaluations

F1. Fasting Glutathione Cycle Biomarkers

Blood, urine, and CNS levels of oxidized and reduced GSH as well as GSH metabolites will be used to evaluate EPI-589 target engagement and ability to correct a key biochemical aspect of disease pathology.

F2. Study Clinical Assessments

The investigator or sub-investigator should be the primary administrator of these assessments, though they may delegate this study procedure to another qualified staff member on their team. It is recommended that the same administrator conduct this assessment on the same patient(s) throughout the study to ensure consistency when at all possible.

a. Parkinson's Disease Rating (MDS-UPDRS)

The MDS-UPDRS is a tool for monitoring the impact of PD, the degree of disability caused, and complications from treatment. Part I evaluates nonmotor experiences of daily living; Part II evaluates motor experiences of daily living; Part III is a motor examination and includes the Hoehn and Yahr scale; Part IV examines motor complications (e.g., motor fluctuations and dyskinesias).

Several questions from Part I and all questions from Part II are designed to be amenable to a patient/caregiver questionnaire format; the remaining interview (Part I and Part III) and examination (Part IV) are designed with the expectation they can be completed within 30 minutes. Each item is measured on a five-point scale.

b. Non-motor Symptoms (NMSS)

Non-motor symptoms are evaluated using the NMSS which is divided into 30 questions in 9 different domains including such symptoms as dribbling saliva, constipation, depression, sleep disorders, apathy, hallucinations and dementia. Symptoms are quantified based on their severity (using a scale of 0 to 3) and frequency (using a scale of 0 to 4). The final cumulative scores are derived from adding up the product of the frequency score times severity score for each of the 30 questions.

c. Parkinson's Disease Questionnaire (PDQ-39)

PDQ-39 is a self-administered questionnaire for patients with PD that has 39 questions relating to eight key areas of health and daily activities, including both motor and non-motor symptoms. It is scored on a scale of 0 to 100, with lower scores indicating better health, and high scores more severe symptoms.

d. EQ-5D

EQ-5D is a questionnaire designed to provide measures of health-related quality of life states, consisting in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

e. Montreal Cognitive Assessment (MoCA)

MoCA is a 30-point questionnaire for cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Severity ranges are approximately: 26 to 30 normal; 18 to 26 mild cognitive impairment; 10-17 moderate cognitive impairment; < 10 severe cognitive impairment.

f. Beck Depression Inventory (BDI)

The BDI is a self-reporting inventory that measures characteristic attitudes and symptoms of depression, including physical symptoms. Twenty-one questions have four responses each (rated 0 to 3) with a total cumulative score scale ranging from 1-10 considered normal) > 40 (extreme depression).

g. Montgomery and Asberg Depression rating scale (MADRS)

The MADRS is a clinician-rated tool for measuring changes in depressive symptom severity. Ten core symptoms and cognitive features are rated on a severity scale of 0 to 6. Higher scores indicate increasing depressive symptoms.

h. Timed motor tests as ON state only (for subjects on dopamine therapy)

Timed motor tests are simple, objective, quantitative measures for the assessment of Parkinson's disease. They include, in an on-medication and an off-medication state, timed recorded physical movements. Since missing dopamine could impair a subject's mobility including their ability to drive the next morning for study visits, the subjects should be encouraged to continue to take their dopamine as prescribed. In order to avoid missing PM dose of the dopamine the previous night, the sites can perform the TUG test on subjects as ON state only.

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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.

A1. Analysis Populations

Demographic characteristics and baseline efficacy data will be presented and summarized by treatment group for all subjects in the efficacy intent to treat (EITT) population. Demographic information will also be summarized by treatment group 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. Fasting blood-based glutathione cycle biomarkers
2. Fasting CNS biomarkers
3. Fasting urine-based biomarkers
4. MDS-UPDRS
5. NMSS
6. PDQ-39
7. EQ-5D
8. MoCA
9. BDI
10. MADRS
11. Timed motor tests as ON state only (for subjects on dopamine therapy)
12. Pharmacokinetics

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 PD.

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 40 subjects (20 with genetically-defined subtypes of PD and 20 idiopathic PD subjects). Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker-responsive idiopathic PD subjects to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the same study protocol and outcome metrics.

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IX. STUDY MEDICATION

A. Description

EPI-589 is presented as an immediate release film-coated tablet. Each tablet contains 250 mg of EPI-589 and the following compendial excipients: lactose, 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, in compliance with 21 CFR 312.6 and Eudralex Vol. 4 EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13

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 HPDE 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]).

C. 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 verification with subject-completed diary cards and returned used drug supply.

D. Drug Accountability

Dosing information will be captured on a subject Dosing Diary Form. This form is part of the 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 Investigator study file to assure the study medication is 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 either be 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 their policies and as detailed below.

B1. Safety Guidance

Based on the known clinical manifestations of Parkinson's disease, we expect that many AEs could occur during the course of the trial that are well documented to occur as the results of the natural history of this disease. These include, but are not limited to worsening neuromuscular function, depression, decline in cognitive function, loss of vision and other ophthalmological symptoms, loss of coordination and loss of speech.

As there are no data available regarding EPI-589 phototoxicity, investigators are to advise subjects to take measures to minimize exposure to ultraviolet (UV) light for the duration of the study and for one week after the last dose.

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 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” or “AE”.

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)

An 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; or
5. A congenital anomaly/birth defect.

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 subject 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 an SAE which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether other AEs, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject, require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

[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; follow-up of the pregnancy, fetus, and child will continue for at least 8 weeks after delivery. While pregnancy itself is not considered an AE or SAE, all pregnancies should be reported using the same process as for SAEs. Any

pregnancy complications or an outcome other than a healthy, normal outcome will be recorded as an AE or SAE.

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.

C3. Non-serious Adverse Event

A non-serious AE 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 and reappears with re-introduction 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 indicated.

Grade 2 – Moderate limitation in activity, some assistance may be needed; minimal noninvasive medical intervention/therapy indicated.

Grade 3 – Severe limitation in activity, assistance usually required; medical intervention/therapy required; hospitalization or prolongation of hospitalization indicated; disabling.

Grade 4 – Extreme limitation in activity, significant assistance required; urgent medical intervention/therapy required; life-threatening consequences.

Grade 5 – Death

C6. Definition of Unexpected Adverse Event

Any AE, the specificity or severity of which is not consistent with those listed in the current investigator's brochure is considered "unexpected."

C7. Notification of SAEs

The Investigator is responsible for promptly notifying the IRB/IEC of all study on-site SAEs 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 MedWatch or CIOMs form (as appropriate).

SAEs (whether unexpected or expected AEs) must be documented on the designated SAE form. The SAE must be reported to the medical expert and appropriate BioElectron Technology Corporation BioElectron-assigned pharmacovigilance staff within 24 hours, according to regulatory, Sponsor, or ICH-E6 Good Clinical Practice, followed by the SAE form within two 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 Investigator and/or Medical Expert must also inform the Study Monitor and the Sponsor in all cases. Any SAEs must also be reported to the IRB/IEC. The Sponsor or designee will ensure that all legal reporting requirements are met.

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 a follow-up SAE forms.

The instructions to sites for the completion of SAE reports give detailed guidance on the reporting of SAEs and AEs initially reported as non-serious that become serious. When a non-serious event becomes serious, details must be forwarded immediately to the Medical expert and BioElectron Technology Corporation or BioElectron-assigned 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 reported to the relevant competent authorities.

In the US, all fatal or life-threatening suspected unexpected serious adverse events assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA as soon as possible (i.e., by telephone or facsimile transmission), but no later than 7 calendar days after first knowledge by the Sponsor that a report qualifies as a suspected unexpected fatal or life-threatening reaction. All unexpected serious adverse events, other than fatal or life-threatening, assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA within 15 calendar days from the day the Sponsor determines that the information qualifies as a SUSAR.

In the UK, the Sponsor or trial investigator must act immediately or at least within 24 hours after becoming aware of a SUSAR by informing the MHRA's Clinical Trial Unit by telephone. The MHRA must then be informed in writing within 3 days of the incident. All SUSARs originating in the UK or originating outside the UK involving the same medicinal product are to be reported. Fatal or life-threatening SUSARs are to be reported as soon as possible, but no later than after 7 days. Any additional relevant information must be sent within 8 days of the report. Non-fatal or non-life-threatening SUSARs are to be reported as soon as possible but no later than 15 days after becoming aware of the reaction.

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. Dose Modification Guidelines

In the event that any patient develops elevated INR ≥ grade 2 in severity (> 1.5-2.5 x ULN) per CTCAE criteria version 4.0 thought to be related to treatment with EPI-589, administration of EPI-589 will be reduced by 1/2 to 50 percent of the starting dose. Should the INR toxicity not resolve to at least grade 1 in severity within two weeks of the initial dose reduction, administration of EPI-589 may either be further reduced or discontinued.

Once a patient's dose is reduced due to elevated INR thought to be related to study drug administration, their dose should not be re-escalated.

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 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.

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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 (0.001%), a systematic review of the database will be undertaken and corrections will be made to achieve an error rate of less than 0.001%.

AEs will be coded using MedDRA, version (14.3). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary, March 2014.

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 or 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, and the General Data Protection Regulation (GDPR).

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 EPI-589-14-01 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 PD. Therefore, we cannot assure that subjects will benefit from treatment with EPI-589. Potential benefits may manifest in a variety of ways, such as in disease-related parameters, functioning, and quality of life.

G3. Risk-Benefit Assessment

There are no effective and/or approved disease modifying treatments available for PD, 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 hold benefit for patients with PD. This is the first study to better understand EPI-589 target engagement and potential therapeutic

benefit in subjects with PD. 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.

This Study is part of a multicenter clinical research study. Accordingly, 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 while this Study is being conducted at other center/s. Only after the completion of this Study at all other centers, provision of the data to the FDA or EMA for review and comment, and publishing the combined data from all of the centers, may the Principal Investigator 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

AE	adverse event
AI	accumulation index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AR	accumulation ratio
BDI	Beck Depression Inventory
BID	twice daily
BSO	L-buthionine-(S,R)-sulfoximine
C-SSRS	Columbia-Suicide Severity Rating Scale
CBC	complete blood count
CFR	Code of Federal Regulations
CK	creatinine kinase
CNS	central nervous system
CoQ10	Coenzyme Q 10
CRF	Case Report Form
CRO	Contract Research Organization
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DaT	dopamine transporters
DSMB	data safety monitoring board
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EITT	efficacy intent-to-treat
EPDA	European Parkinson's Disease Association
EU	European Union
%F	percent fluctuation
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GCRC	good clinical research practice
GDPR	General Data Protection Regulation
GSH	glutathione
GSSG	glutathione disulfide
HDPE	high density polyethylene
hERG	human Ether-a-go-go Related Gene
HCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HMPAO	hexamethylpropylene amine oxime
ICF	informed consent form
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUPAC	International Union of Pure and Applied Chemistry

kg	kilogram
Λz	apparent terminal constant
LFT	liver function test
MAD	multiple ascending (oral) dose
MADRS	Montgomery and Asberg Depression rating scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
mg	milligram
mL	milliliter
MoCA	Montreal Cognitive Assessment
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPV	mean platelet volume
mtDNA	mitochondrial DNA
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NF	National Formulary
nM	nanomolar
NMSS	Non-motor Symptoms Scale
NOAEL	no observed adverse effect level
NQ01	NAD(P)H Quinone oxidoreductase 1
OD	once daily
OTC	over-the-counter
PD	Parkinson’s disease
PDQ-39	39-Item Parkinson’s Disease Questionnaire
PO	by mouth
PT	Prothrombin Time
PTT	Partial Prothrombin 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
SAD	single ascending (oral) dose
SAE	serious adverse event
SD	standard deviation
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
UV	ultraviolet

XIV. SIGNATURE OF SPONSOR

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: 2 q S v{l r 2,-cl-,Signature: [redacted]

[redacted]

BioElectron Technology Corporation
350 North Bernardo Ave
Mountain View, CA 94043

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Summary of Changes
Amendment 5.0
EPI589-15-002

A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects

Protocol Number	EPI589-15-002
Original Protocol Date	27 April 2015
Amendment 1.0 Date	09 September 2015
Amendment 2.0 Date	04 January 2016
Amendment 3.0 Date	10 October 2016
Amendment 4.0 Date	17 February 2017
Amendment 5.0 Date	29 September2017
Study Sponsor	BioElectron Technology Corporation 350 North Bernardo Avenue Mountain View, CA 94043
Sponsor's Representative	[redacted] BioElectron Technology Corporation 350 North Bernardo Avenue Mountain View, CA 94043

Amendment 5.0 provides the following change and rationale:

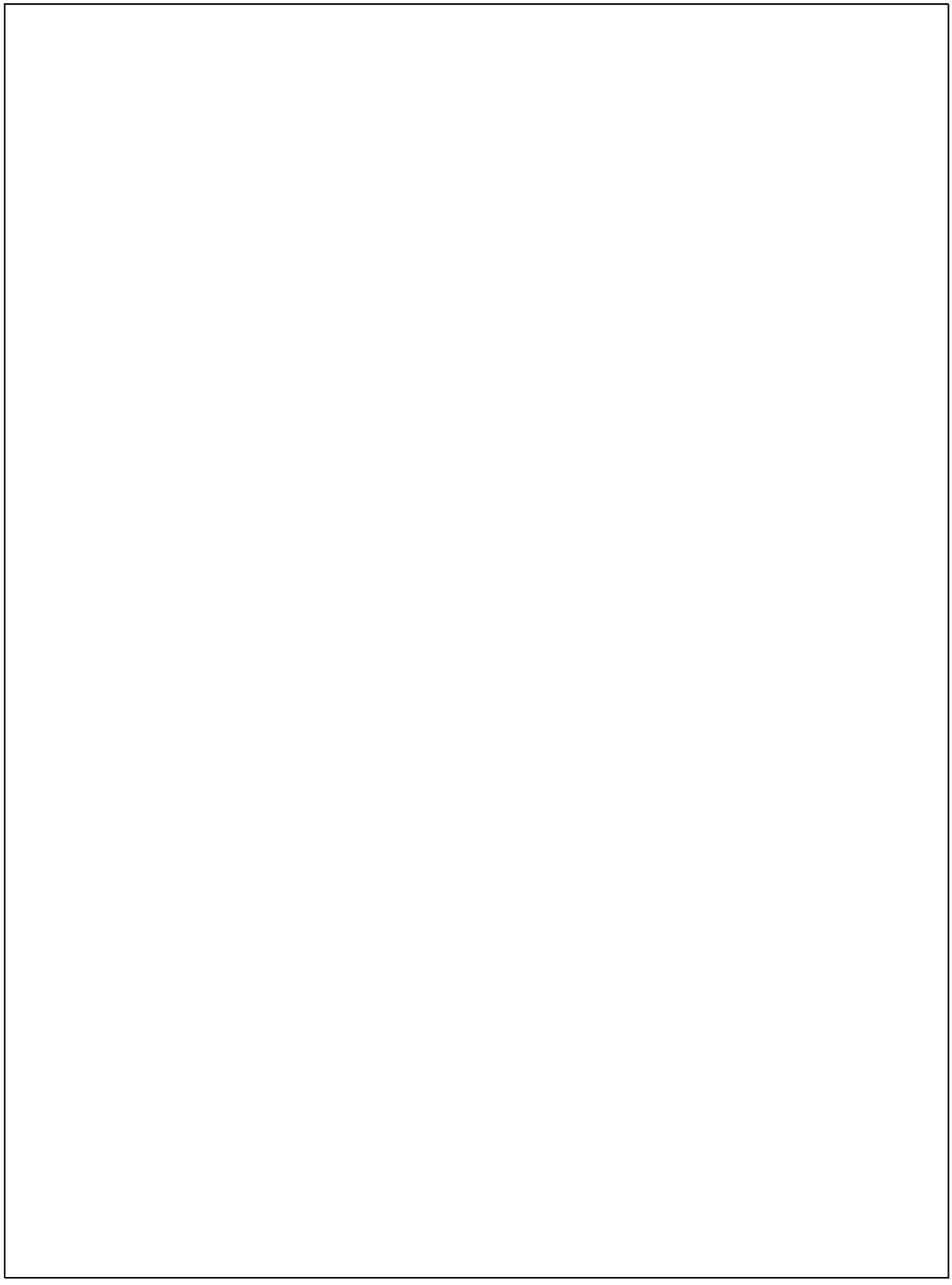
Change	Rationale
1. Fasting conditions for biomarker samples	To clarify that biomarker samples should be fasting samples.
2. Added the term morning and evening dose to BID	To provide further clarification that dosing is twice daily rather than every 12 hours.
3. Non-clinical studies language	To provide updated information on nonclinical studies.
4. Changed the language under pharmacokinetics (PK) section	To clearly define the expected number of PK blood draws
5. Changed the timed motor test as ON state only (for subjects on dopamine therapy)	To clarify that sites can perform TUG test on subjects in ON state only
6. Dose Limiting Toxicity	To provide clear definition for dose limiting toxicities (DLTs)
7. Administration of clinical assessment	To clarify the primary administrator of the PD assessments for the study
8. Washout period for subjects on high doses of Vitamin E or C	To clarify the need for a 2 week wash out prior to enrollment for subjects on higher doses of vitamin C and E supplements
9. CBC differential as absolute or percentages	For better clarity about recording the values
10. CO_2 for serum chemistry	CO_2 is taken and assessed as biocarbonate in most clinical labs. Hence replaced the term Co2 as bicarbonate in the protocol. This is a venous sample.
11. Day 1 first dose language	To clarify that first dose may be taken same day as baseline visit after completing all assessments
12. Changed the height measurement to screening visit only	To clarify that height measurement need not be repeated after screening visit
13. Included breast exam as part of screening physical exam	To capture the findings from breast exam as part of the screening physical exam
14. Removed language in adverse event reporting	To clarify reporting for adverse events
15. Changed the AE language under post-treatment follow up	To clearly define the post treatment follow-up to be at least 10 days after last dose and if there are any ongoing or new AEs noted at month 3, then the follow up will be up to 30 days after last dose

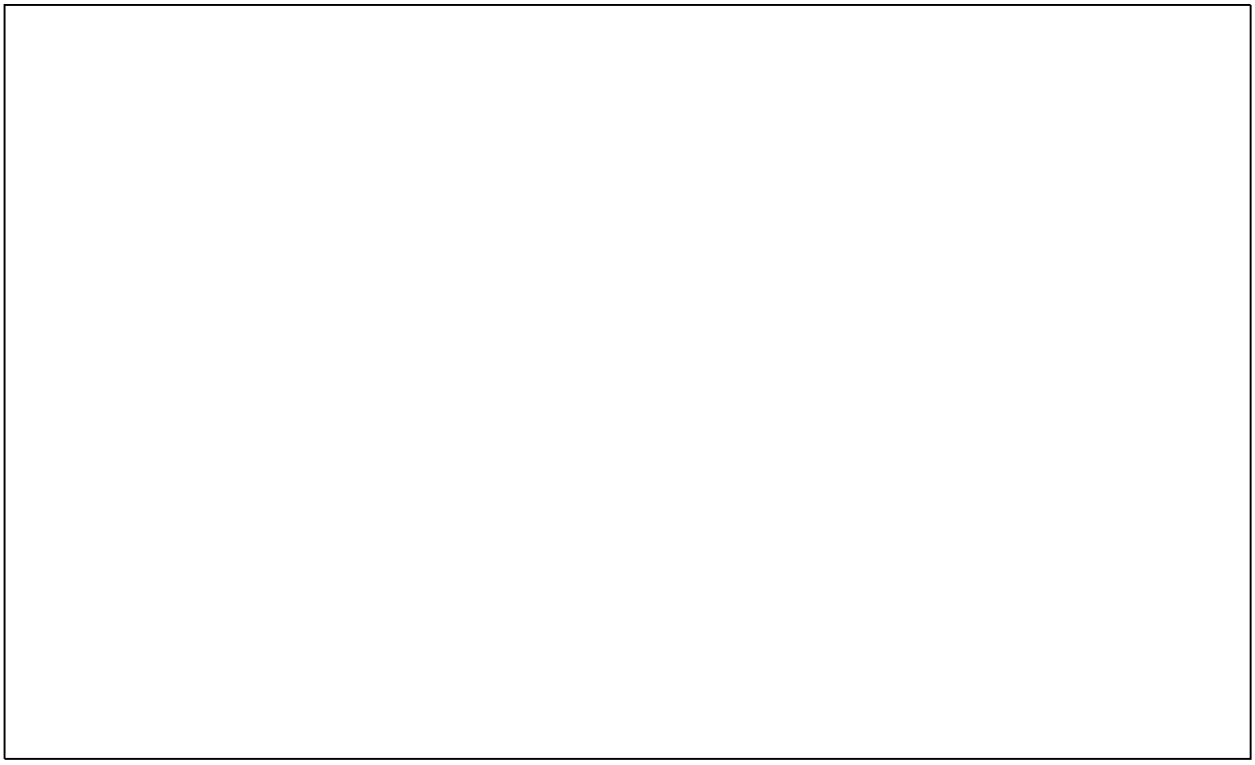
DESCRIPTION OF CHANGES TO THE PROTOCOL

Changes to the protocol by section appear in the table below. Administrative and editorial clarifications, corrections or adjustments may not be individually identified.

In this summary document, ***bold italic*** font indicates additions to existing text, and ~~strikethrough~~ font indicates deleted text. The actual amended protocol does not include bold or strikethrough font to indicate changes.

Protocol Section	Modification
I. Synopsis Study Objectives	Secondary Objectives To evaluate the effects of EPI-589 in subjects with PD on: 1. ***Fasting*** ~~G~~glutathione cycle biomarkers as measured in blood, cerebral spinal fluid, and urine
I. Synopsis Test product, mode of administration and dose	Dose EPI-589 500-mg BID ***(morning and evening dose along with food)***
I. Synopsis Efficacy variables	1. **Fasting** ~~B~~***b***lood-based glutathione biomarkers 2. **Fasting** CNS biomarkers 3. **Fasting** ~~U~~***u***rine-based biomarkers 11. Timed motor tests in ON ~~and OFF~~ state ***only*** (for subjects on dopamine therapy)
IV. Study Objectives B. Safety Variables	Clinical 1. Routine assessments of AEs and SAEs 2. Dose limiting toxicities 3. Electrocardiogram 4. C-SSRS 5. ~~Laboratory~~ 6. Routine serum chemistries with liver function tests 7. Routine hematology tests with coagulation tests





III. Introduction	~~*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. In 28-day and 91-day repeat-dose toxicity studies in rat and cynomolgus monkey, the no observed adverse effect level (NOAEL) was 300 mg/kg/day, corresponding to combined mean Cmax values of 37,717 to 56,500 ng/mL (rat) and 14,300 to 16,417 ng/mL (monkey), and a combined mean area under the plasma concentration-time curve from time zero to the last measurable concentration (AUClast) value of 149,495 to 297,000 ng.h/mL (rat) and 47,300 to 67,656 ng.h/mL (monkey) (Studies 1660-038, 1660-039, 1660-063, and 1660-064).~~ ~~A phase 1 clinical study demonstrated that healthy subjects administered 500 mg EPI-589 BID for 14 days showed a mean Cmax value of 1,890 ng/mL and a mean AUClast value of 5,240 ng.h/mL (Study EPI589-14-01). These plasma concentrations are well below the mean exposure values in monkey associated with the NOAEL in the toxicity studies, corresponding to safety margins of approximately 7- to 8-fold for the mean Cmax and 9- to 12-fold for the mean AUC.~~ ~~During the 28-day repeat-dose toxicity studies, rat and monkey were exposed to up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-039 and 1660-038). The NOAEL for both studies was 300 mg/kg/day. Rats exposed to 1,000 mg/kg/day exhibited adverse 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 showing corresponding microscopic pathology. The majority of these findings were resolved following the 28-day recovery period. Monkeys exposed to 1,000 mg/kg/day showed significant test-article related morbundity that resulted in half the animals in the high dose group being euthanized on Days 3 and 4 and the remaining animals being euthanized on Day 9. These animals exhibited significant elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values, and microscopic findings in the kidney, liver, skeletal muscle, heart, and lymphoid tissues. In several of the animals the primary cause of morbidity was determined to be test-article related renal tubular degeneration/necrosis.~~ ~~During the 91-day repeat-dose toxicity studies, rat and monkey were exposed to up to 300 mg/kg/day EPI-589 PO (Studies 1660-063 and 1660-064). The NOAEL for the rat study was 300 mg/kg/day and the no observed effect level (NOEL) for the monkey study was 300 mg/kg/day. Male rats exposed to 300 mg/kg/day and female rats exposed to ≥ 100 mg/kg/day exhibited mild test-article related effects on hematology parameters consistent with hemolysis and bone marrow regeneration. These findings were not considered adverse.~~ ~~Development and reproductive toxicology studies were conducted in rat and rabbit at doses up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-069, 1660-067, and 1660-068). The NOAEL for reproductive toxicity in rat was demonstrated to be 1,000 mg/kg/day (1660-069). The NOAEL for developmental toxicity in rat and rabbit during the embryofetal studies was deemed to be 300 mg/kg/day (Studies 1660-067 and 1660-068).~~

	~~Rats exposed to 1,000 mg/kg/day exhibited 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. Rabbits exposed to 1,000 mg/kg/day exhibited 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 (Study EPI589-14-01) and rabbits exposed to 1,000 and 300 mg/kg/day EPI 589 is approximately 179 to 236 fold and 47 to 50 fold, respectively. 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 (Study AD58AS.502ICH.BTL); 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 (Study AD58AS.331ICH.BTL); and negative in the in vivo micronucleus assay in rat (Study AD58AS.125012ICH.BTL). These data indicate a low clinical mutagenicity risk.~~ ~~Primary pharmacodynamics studies demonstrated that EPI 589 is a potent rescue agent in cellular models of diseases of energy metabolism and oxidative stress. In vitro cellular models utilizing primary human fibroblasts from patients with ALS, Parkinson's disease and other diseases characterized by high levels of oxidative stress, or striatal cells derived from mouse models of Huntingdon's disease were used to assess the potential of EPI 589 to mitigate the harmful effects of oxidative stress (Studies EPI BA 000216, EPI BA 000363, and EPI BA 000362).~~ ~~Pretreatment of patient cells with EPI 589 potently protected against oxidative stress mediated cell death in a concentration dependent manner. Furthermore, EPI 589 normalized 3 nitrosotyrosine (3NT) levels, a biomarker of oxidative stress, and increased glutathione levels in mouse striatal cells under oxidative stress conditions.~~ ~~In secondary pharmacodynamics in vitro receptor/ion channel binding studies, EPI 589 did not significantly affect off target molecular targets (Study EPI BA 159). In safety pharmacology studies, EPI 589 did not significantly affect ion channel current in the hERG assay (Study 130719.FEK); did not affect ECG parameters during the 28 day and 3 month repeat dose toxicology studies in monkey at doses up to 1,000 mg/kg/day (only Day 1 data collected for animals administered 1,000 mg/kg/day and up to Day 91 data collected for animals administered up to 300 mg/kg/day) (Studies 1660 038 and 1660 064); and did not change respiratory function or adversely impact neurobehavioral function in rat at doses up to 1,000 mg/kg (Studies 1660 051, 1660 050, and 1660 063).~~ ~~In single dose exposure PK studies, EPI 589 was absorbed rapidly in rat, dog, and monkey, with mean Tmax values ranging from .08 to 1 hour and mean T1/2 values ranging from 3.7 to 5.0 hours (Studies EPI BA 53, EPI BA 59, EPI BA 72, and EPI BA 302). EPI 589 does not significantly induce cytochrome P450 (CYP) enzymes and appears to be metabolized by reductases in the liver cytosol~~

~~and microsomal subcellular fractions and to a lesser extent by the family of CYP enzymes (Studies MC12M 0037 and MC14M 0018).~~
~~EPI-589 exhibited weak direct inhibition of CYP2B6, CYP2C8, CYP2C9, and CYP3A4/5 (both midazolam and testosterone as probe substrates) with estimated IC50 (µM) values and R values based on free plasma concentrations (shown in parentheses) of 28 (1.25), 40 (1.18), 92 (1.08), 34 (1.21), and 53 (1.13), respectively (Study MC14M 0020)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 is an orally available compound that has been demonstrated in vitro and in vivo to cross the blood-brain-barrier. In 28-day, 91-day, 6-month, and 9-month repeat-dose toxicity studies in rat and cynomolgus monkey, the no observed adverse effect level (NOAEL) was 300 mg/kg/day, corresponding to terminal combined mean C_{max} values of 37,717 to 56,500 ng/mL (rat) and 14,300 to 24,500 ng/mL (monkey), and terminal combined mean area under the plasma concentration-time curve (AUC) values of 149,495 to 297,000 ng.h/mL (rat) and 47,300 to 124,000 ng.h/mL (monkey) (Studies 1660-038, 1660-039, 1660-063, 1660-064, 1660-079, and 1660-080).

The dose-limiting drug-associated toxicity observed in the 28-day, 3-month, and 9-month (monkey) animal studies was hemolysis in rat and significant acute toxicity leading to moribundity with indication of skeletal, renal, liver, and lymphoid tissue effects in monkey. All clinical program investigators have been required to monitor hematology parameters and clinical chemistry parameters for kidney, liver, and muscle function in all EPI-589 subjects. To date, no dose-limiting toxicities have been reported with EPI-589 in humans.

A phase 1 clinical study demonstrated that healthy young and elderly subjects administered 500 mg EPI-589 BID for 14 days showed mean C_{max} values of 1,890 to 1,960 ng/mL and mean AUC values of 10,480 to 11,000 ng.h/mL (Study EPI589-14-01). These plasma concentrations are well below the 300 mg/kg/day NOAEL exposure values in monkey, the most sensitive toxicity species, corresponding to repeat-dose exposure safety margins of approximately 7- to 12- fold for the mean C_{max} and 4- to 8-fold for the mean AUC.

During the 9-month repeat-dose toxicity study in monkey, animals were administered 60, 100, 300, or 500 mg/kg/day EPI-589 PO (Study 1660-080). The NOAEL was 300 mg/kg/day. Monkeys that received 500 mg/kg/day showed significant test-article related moribundity after receiving only three or four doses resulting in three animals being euthanized on Days 4, 5, and 7 and the remaining animals being euthanized on Day 11

	Animals exhibited significant elevations in AST and ALT values, and microscopic findings in multiple sites in the skeletal muscle, kidney, liver, and lymphoid tissues. The primary cause of morbidity in the three animals euthanized on Days 4, 5, and 7 was myofiber degeneration and degenerative changes in kidney (3/3 animals). The toxicity observed following administration of three to four doses of 500 mg/kg/day EPI-589 were similar and consistent with toxicity observed following administration of two doses of 1,000 mg/kg/day during the 28-day toxicity study (Study 1660-038), likely due to similar exposures between the two doses. The margin of exposure between healthy young and elderly humans exposed to 500 mg BID EPI-589 (relevant clinical dose) for 14 days (Study EPI589-14-01) and monkeys exposed to EPI-589 PO on Day 1 is approximately 26-fold for the mean C_{max} and 21-fold for the mean AUC_{last} at 500 mg/kg, and approximately 29-fold for the mean C_{max} and 27-fold for the mean AUC_{last} at 1,000 mg/kg. ***During the 6-month repeat-dose toxicity study in rat, animals were exposed to up to 300 mg/kg/day EPI-589 PO (Study 1660-079). The NOAEL was 300 mg/kg/day. Rats exposed to 300 mg/kg/day exhibited mild test-article related effects on hematology parameters consistent with hemolysis and compensating reticulocytosis. These findings were not considered adverse.*** ***During the 91-day repeat-dose toxicity studies, rat and monkey were exposed to up to 300 mg/kg/day EPI-589 PO (Studies 1660-063 and 1660-064). The NOAEL for the rat study was 300 mg/kg/day and the no observed effect level (NOEL) for the monkey study was 300 mg/kg/day. Male rats exposed to 300 mg/kg/day and female rats exposed to ≥ 100 mg/kg/day exhibited mild test-article related effects on hematology parameters consistent with hemolysis and bone marrow regeneration. These findings were not considered adverse.*** ***During the 28-day repeat-dose toxicity studies, rat and monkey were exposed to up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-039 and 1660-038). The NOAEL for both studies was 300 mg/kg/day. Rats exposed to 1,000 mg/kg/day exhibited adverse 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 showing corresponding microscopic pathology. The majority of these findings were resolved following the 28-day recovery period. Monkeys exposed to 1,000 mg/kg/day showed significant test-article related moribundity after receiving only two doses resulting in half the animals in the high dose group being euthanized on Days 3 and 4 and the remaining animals being euthanized on Day 9. Animals exhibited significant elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values, and microscopic findings in multiple sites in the skeletal muscle, kidney, liver, lymphoid tissues, and heart. The primary cause of morbidity in five animals euthanized on Days 3 and 4 was renal tubular degeneration and necrosis (2/5 animals) or was not able to be determined (3/5 animals).***

	Development and reproductive toxicology studies were conducted in rat and rabbit at doses up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-069, 1660-067, and 1660-068). The NOAEL for reproductive toxicity in rat was demonstrated to be 1,000 mg/kg/day (Study 1660-069). The NOAEL for developmental toxicity in rat and rabbit during the embryofetal studies was deemed to be 300 mg/kg/day (Studies 1660-067 and 1660-068). Rats exposed to 1,000 mg/kg/day exhibited 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. Rabbits exposed to 1,000 mg/kg/day exhibited 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 young and elderly humans exposed to 500 mg BID EPI-589 (relevant clinical dose) for 14 days (Study EPI589-14-01) and rabbits exposed to 300 or 1,000 mg/kg/day EPI-589 is approximately 22-fold and 84-fold, respectively. 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 (Study AD58AS.502ICH.BTL); 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 (Study AD58AS.331ICH.BTL); and negative in the in vivo micronucleus assay in rat (Study AD58AS.125012ICH.BTL). These data indicate a low clinical mutagenicity risk.*** ***In secondary pharmacodynamics in vitro receptor/ion channel binding studies, EPI-589 did not significantly affect off-target molecular targets (Study EPI-BA-186). In safety pharmacology studies, EPI-589 did not significantly affect ion channel current in the human ether-a-go-go-related gene (hERG) assay (Study 130719.FEK); did not adversely affect electrocardiogram (ECG) parameters during the 28-day, 3-month, or 39-week repeat-dose toxicology studies in monkey at doses up to 1,000 mg/kg/day (only Day 1 data collected for animals administered 500 or 1,000 mg/kg/day and up to Day 91 data collected for animals administered up to 300 mg/kg/day) (Studies 1660-038, 1660-064, and 1660-080); and did not change respiratory function or adversely impact neurobehavioral function in rat at doses up to 1,000 mg/kg (Studies 1660-051, 1660-050, and 1660-063).*** ***EPI-589 is approximately 60% protein bound in human plasma (Study MC14M-0067). EPI-589 did not significantly induce cytochrome P450 (CYP) enzymes (Study MC12M-0037) and exhibited weak direct inhibition of CYP2B6, CYP2C8, CYP2C9, and CYP3A4/5 (both midazolam and testosterone as probe***

	substrates) with estimated IC_{50} (µM) values and R values based on free plasma concentrations (shown in parentheses) of 28 (1.25), 40 (1.18), 92 (1.08), 34 (1.21), and 53 (1.13), respectively (Study MC14M-0020). EPI-589 is metabolized by reductases in the liver cytosol and microsomal subcellular fractions, and to a lesser extent by the family of CYP enzymes (Study MC14M-0018). EPI-589 is an inhibitor of the BCRP efflux transporter, possibly an inhibitor of the MATE1, OATP1B3, MATE2-K, OCT1, OATP1B1, OCT2 and OAT3 uptake transporters (in order of increasing inhibitory potential), and possibly a substrate of the MDR1 and BCRP efflux transporters (Edison-04-25Feb2014). ***An in vivo primary pharmacodynamic study demonstrated that EPI-589 significantly reduced disease progression as measured by standard functional outcomes of rotarod test and forelimb deformity score as compared with vehicle controls in the gold standard in vivo wobbler mouse model of ALS. These EPI-589 effects were superior to riluzole. In addition, EPI-589 had synergistic effects with riluzole when co-administered. These results indicate that EPI-589, alone or in combination with riluzole, may have beneficial effects on the progression of neuromuscular dysfunction in ALS patients (Study R-PH-EPI-589-002).*** ***In vitro primary pharmacodynamics studies demonstrated EPI-589 is a potent rescue agent in cellular models of diseases of energy metabolism and oxidative stress. In vitro cellular models utilizing primary human fibroblasts from patients with ALS, Parkinson's disease and other diseases characterized by high levels of oxidative stress, or striatal cells derived from mouse models of Huntingdon's disease were used to assess the potential of EPI-589 to mitigate the harmful effects of oxidative stress (Studies EPI-BA-000216, EPI-BA-000363, and EPI-BA-000362). Pretreatment of patient cells with EPI-589 potently protected against oxidative stress-mediated cell death in a concentration dependent manner. Furthermore, EPI-589 normalized 3-nitrosotyrosine (3NT) levels, a biomarker of oxidative stress, and increased glutathione levels in mouse striatal cells under oxidative stress conditions.*** ***The nonclinical laboratory studies conducted in accordance with the United States Food and Drug Administration (FDA) Good Laboratory Practice (GLP) Regulations 21 Code of Federal Regulations (CFR) Part 58 were conducted in conformance with the principles of OECD-GLP in the United States, a country that is part of the OECD Mutual Acceptance of Data process.***

IV. Study Objectives B. Secondary Objectives	The secondary objectives are to evaluate the effects of EPI-589 in subjects with PD on: ***Fasting*** ~~***G****g*~~***lutathione*** cycle biomarkers as measured in blood, cerebral spinal fluid, and urine
V. Investigational Plan A4. Treatment Phase	EPI-589 dosing will start on Day 1. Subjects will self-administer EPI-589 at a dose of 500-mg BID ***(morning and evening dose along with food)***
V. Investigational Plan A4. Post-Treatment Follow-up	Post-Treatment Follow-up will be at least 10 days ***after last dose*** and ***if there are any ongoing or new AEs noted at month 3 then the follow up will be*** up to 30 days after last dose: AE/SAE and concomitant medication assessments conducted by telephone. Additional assessments to be determined at Investigator discretion.
VI. Study Procedures A. Screening Visit	4. Physical examination***** including vital signs 5. Height****** and Weight 7. Laboratory assessments for hematology, coagulation, and serum chemistry******* **** Breast exam is at screening physical exam only.*** *****Height is measured at screening visit only.*** ****** Screening values can be used if done within one month of baseline and if completed under fasted conditions***
VI. Study Procedures A1. Run-In Assessments	1. ***Fasting*** ~~***B****b****l****ood***~~-based glutathione cycle biomarkers 2. ***Fasting*** CNS biomarkers (lumbar puncture) 3. ***Fasting*** ~~***U****u****r****ine***~~ biomarkers

VI. Study Procedures Treatment Phase	After the Run-in phase, the subject must return to the clinic within 30 days (± 3 days) for baseline assessments. In-clinic study visits are scheduled at Month 1 and Month 3. The Month 2 study assessments can be conducted via telephone. End of treatment assessments will be conducted at the Month 3 study visit. Pharmacokinetic sampling takes place at Month 1 and Month 3. ***The baseline and all subsequent laboratory assessments should be obtained under fasting conditions.*** B1. Baseline Assessments The following will be assessed or performed at this visit. 4. ***Fasting*** ~~B~~*b*lood-based GSH cycle biomarkers 5. ***Fasting*** ~~U~~*u*rine-based biomarkers 6. Laboratory assessments for hematology, coagulation and serum chemistry* *Screening results for these assessments may be used if obtained within 1 month of Baseline and if they are completed under fasted conditions. ***The baseline laboratory assessments should be obtained under fasting conditions.***
VI. Study Procedures B2. Study Visit Assessments	Month 1 Clinic Visit (Day 29 ± 3 days) The following will be assessed or performed at the <u>Month 1</u> clinic visit: 7. Laboratory assessments for hematology, coagulation, and serum chemistry* 8. ***Fasting*** ~~B~~*b*lood-based GSH cycle biomarkers 9. ***Fasting*** ~~U~~*u*rine-based biomarkers ***10.*** Pharmacokinetics**: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing. ***12 hour time point may be obtained at 0 hour.*** ****The laboratory assessments should be obtained under fasting conditions.***

VI. Study Procedures B2. Study Visit Assessments	Month 3 Clinic Visit (Day 85 ± 3 days) The following will be assessed or performed at the Month 3 clinic visit: 7. Laboratory assessments for hematology, coagulation, and serum chemistry* 8. ***Fasting*** ~~B~~*b*lood-based GSH cycle biomarkers 9. ***Fasting*** ~~U~~*u*rine-based biomarkers 10. ***Fasting*** CNS biomarkers ***13.*** Pharmacokinetics**: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.***12 hour time point may be obtained at 0 hour.*** ****The laboratory assessments should be obtained under fasting conditions.***
VI. Study Procedures B3. Pharmacokinetics	Plasma concentration samples will be collected from ***20 subjects (10 idiopathic and 10 with genetically defined subtypes)*** ~~the first 10 subjects to complete 1 month of therapy at each site~~, at the following time points: • Month 1 (Day 29 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose • Month 3 (Day 85 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose ** 12 hour PK can be obtained at time 0 ***The pharmacokinetics samples collection will be monitored as subjects are enrolling and Sponsor will alert each principal investigator once the required samples for each subtype are obtained.***
VI. Study Procedures H. 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. ***However if the subjects are on high doses of Vitamin E and C and are eligible to participate , they are allowed a 2 weeks washout period prior to enrollment.*** 2. Participation 3 months prior to and for the duration of the study in a trial of a device, drug or other therapy for PD

VII. Study Endpoints and Evaluations B. Secondary Endpoints (Efficacy)	1. **Fasting** ~~B~~***b***lood-based glutathione biomarkers 2. **Fasting** CNS biomarkers 3. **Fasting** ~~U~~***u***rine-based biomarkers 11. Timed motor tests in ON ~~and OFF~~ state ***only*** (for subjects on dopamine therapy)
VII. Study Endpoints and Evaluations	D1. Physical Examination, ***height and weight*** Complete physical exams will be conducted (excluding genital/rectal exam) at protocol specified study visits. 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, heart, abdomen, and extremities. 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). ***The findings from breast exam will be captured as part of the screening physical exam. The findings from breast exams conducted within 6 months of the screening visit and those collected as part of medical history, may be used for the screening physical exam***. Medical history and demographics including age, gender, race, ~~height and weight~~ will be collected at Screening. ~~*D2. Height and Weight*~~ Weight (kg) will be measured in ordinary indoor clothing (i.e., street clothes, scrubs, etc.) with shoes off. Height will be recorded in centimeters (cm) ***and need not be repeated after screening visit.*** 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.

VII. Study Endpoints and Evaluations D2. Laboratory Evaluations	a. Hematology ***a.*** Leukocytes: white blood cell count (WBC) and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils). ***The differential can be recorded as an absolute value or percentages.*** b. Serum Chemistry c. Electrolytes: sodium, potassium, chloride and ~~carbon dioxide (CO_2)~~ ***bicarbonate***
VII. Study Endpoints and Evaluations D3. Dose Limiting Toxicity (DLT)	***There were no DLTs noted in the phase 1 study; the dose-limiting (NOAEL) in nonclinical studies, as described in the protocol were increased LFTs (ALT, AST), rhabdomyolysis (elevated CPK), renal dysfunction (likely secondary to rhabdo), and marrow toxicity (most notably hemolysis). Therefore for this study, any increased LFT, BUN/Cr or CPK (or CK) should be considered related to study drug and should be designated as a DLT. If there is a DLT, a dose reduction will be attempted. Contact the medical monitor for further instructions.***
VII. Study Endpoints and Evaluations F. Efficacy Evaluations	F1. ***Fasting*** Glutathione Cycle Biomarkers
VII. Study Endpoints and Evaluations F. Efficacy Evaluations	F2. Study Clinical Assessments ***The investigator or sub-investigator should be the primary administrator of these assessments, though they may delegate this study procedure to another qualified staff member on their team. It is recommended that the same administrator conduct this assessment on the same patient(s) throughout the study to ensure consistency when at all possible.***

VII. Study Endpoints and Evaluations F2. Administration of Study Clinical Assessments	h. Timed Motor Tests in ON ~~and OFF~~ state ***only*** (for subjects on dopamine therapy) Timed motor tests are simple, objective, quantitative measures for the assessment of Parkinson's disease. They include, in an on-medication and an off-medication state, timed recorded physical movements. ***Since missing dopamine could impair a subject's mobility including their ability to drive the next morning for study visits, the subjects should be encouraged to continue to take their dopamine as prescribed. In order to avoid missing PM dose of the dopamine the previous night, the sites can perform the TUG test on subjects as ON state only.***
VIII. Statistical Considerations C. Efficacy Analysis	1. **Fasting** ~~B~~***b***lood-based glutathione biomarkers 2. **Fasting** CNS biomarkers 3. **Fasting** ~~U~~***u***rine-based biomarkers 11. Timed motor tests in ON ~~and OFF~~ state ***only*** (for subjects on dopamine therapy)
X. Safety Management	B. Adverse Event Reporting All SAEs will be reported to the IRB/***IEC*** in accordance with their ~~the IRB~~ policies and as detailed below. ~~AEs that are not serious will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.~~
	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.

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EPI589-15-002

A Phase 2A Safety and Biomarker Study of **EPI-589 in Mitochondrial** Subtype and Idiopathic Parkinson's Disease Subjects

Original Protocol:	27 April 2015
Protocol Amendment 1.0:	09 September 2015
Protocol Amendment 2.0:	04 January 2016
Protocol Amendment 3.0:	10 October 2016
Protocol Amendment 4.0:	17 February 2017

BioElectron Technology Corporation
350 North Bernardo Avenue
Mountain View, CA 94043

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I. PROTOCOL SYNOPSIS

Title of study	A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects
Protocol number	EPI589-15-002
IND number	126,795
EudraCT number	2015-001786-10
Original Protocol	27 April 2015
Protocol Amendment 1.0	09 September 2015
Protocol Amendment 2.0	04 January 2016
Protocol Amendment 3.0	10 October 2016
Protocol Amendment 4.0	17 February 2017
Investigative Drug	EPI-589
Study Sponsor	BioElectron Technology Corporation 350 North Bernardo Avenue Mountain View, CA 94043
Investigators and Investigative Sites	• [redacted] USA • [redacted] USA • [redacted] UK • [redacted] USA • [redacted] Germany
Study population	Approximately 40 subjects with Parkinson's disease (PD) including 20 subjects with genetically-defined subtypes

Rationale for Study	Mitochondrial pathophysiology It is now well appreciated that defects in mitochondrial function contribute to the pathophysiology of PD both in subjects with defined genetic defects as well as those with idiopathic forms of the disease. High morbidity Despite the available therapies for symptomatic relief, PD remains a highly morbid disease. There are no approved treatments for PD capable of modifying disease progression. Pre-clinical efficacy data EPI-589 is a redox active molecule that has demonstrated potency (EC50 < 100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with idiopathic and familial PD subtypes including PINK1, parkin and LRRK2.
Study objectives	Primary Objective To evaluate the effects of EPI-589 on safety as assessed by occurrence of drug-related serious adverse events in subjects with PD. Secondary Objectives To evaluate the effects of EPI-589 in subjects with PD on: 1. Glutathione cycle biomarkers as measured in blood, cerebral spinal fluid, and urine 2. Clinical disease state as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) 3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D 4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA) and 5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery and Asberg Depression rating scale (MADRS) 6. Pharmacokinetics 7. Hematology, blood chemistry, electrocardiogram

Study design	Open-label study with 30-day run-in phase.
Planned number of subjects	Approximately 40 subjects (20 with genetically-defined subtypes of PD and 20 idiopathic PD subjects). (Adaptive design component allows enrollment of up to 20 additional subjects with idiopathic PD to try to achieve a total of 20 subjects that have a biomarker response to EPI-589.)
Study duration	3 months (85 days ± 3 days) of study treatment preceded by a 1-month baseline parameter run-in period.
Test product, mode of administration, and dose	Test product EPI-589 in a tablet formulation at a strength of 250 mg Mode of Administration Oral with meal Dose EPI-589 500-mg BID
Reference therapy, dose, and mode of administration	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 (all subjects)	1. Hoehn and Yahr stage ≤ 3.0 2. Ambulatory with or without assistance 3. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., hormonal methods, including oral, subcutaneous, and intrauterine; barrier methods, including [redacted] condom, [redacted] condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study treatment. 4. Willingness and ability to comply with study procedures

5. If on medications for PD drugs, then medication regimen must be stable for 60 days prior to enrollment
6. Abstention from use of other investigative or non-approved drugs for the duration of the trial

For Idiopathic Subjects

7. A diagnosis of idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit
8. Age 40 to 75 years
9. Within 5 years of diagnosis of Parkinson's disease

For Genetic Subtype Subjects

10. A confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LRRK2 or other mitochondrial genetic subtype
11. Age 21 to 75 years

Exclusion criteria

1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation
2. Use of antioxidant supplements, specifically vitamins E and C beyond the recommended daily allowance
3. Other Parkinsonian disorders
4. MoCA score of <24
5. Revised Hamilton Rating Scale for Depression ≥ 11
6. Parkinsonism due to drugs or toxins
7. Diagnosis of any other clinically significant neurologic disease that will confound the assessment of effect of study drug on disease progression
8. Malignancy within past two years
9. Pregnant or plans to become pregnant or breast feeding
10. History of stroke
11. History of brain surgery
12. Hepatic insufficiency with liver function tests (LFTs) > 3 times upper limit of normal
13. Renal insufficiency as defined by creatinine > 1.5 times normal
14. End stage cardiac failure
15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD

Treatment	Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues. Post-treatment follow-up will be at least 10 days and up to 30 days after last dose.
Efficacy variables	1. Blood-based glutathione biomarkers 2. CNS biomarkers 3. Urine-based biomarkers 4. MDS-UPDRS 5. Non-motor Symptoms Scale (NMSS) 6. PDQ-39 7. EQ-5D 8. MoCA 9. Beck Depression Inventory (BDI) 10. Montgomery & Asberg Depression rating scale (MADRS) 11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy) 12. Pharmacokinetics
Safety variables	Clinical 1. Routine assessments of AEs and SAEs 2. Dose limiting toxicities 3. Electrocardiogram 4. C-SSRS 5. Laboratory 6. Routine serum chemistries with liver function tests 7. Routine hematology tests with coagulation tests
Statistical Considerations	<u>Data Analysis</u> This is a within-subject, controlled open-label study seeking to determine the safety and tolerability of EPI-589 in patients with PD as well as to determine if EPI-589 can alter the biochemical signature of PD as assessed by peripheral blood biomarkers, CNS biomarkers, brain imaging biomarkers, and urine biomarker analysis. In addition, data on a number of disease-relevant clinical measures will be collected.

II. SCHEDULE OF ASSESSMENTS AND DOSING SCHEDULE

Tests	-2 to -1 Months		DayO		Month 1	Month 2	Month3 End of Treatment Visit	Post-Treatment Follow-up
	Screening	Run-in (upto 30 days from screenin2)	Baseline (27-33 days from run-in		Day29 (± 3 days)	Day 57d (±3 days)	Day85 (±3 days)	Up to 30Days afte1·Last Dose•
Informed consent				Day 1 First Dose				
Inclusion/Exclusion criteria								
Past Medical history								
Pre:wous genetic testing review								
Physical exam & Vital signs								
Height & weight			-					
12-lead ECG			-					
Hematology (including coagulation panel)			-		f		f	
Semm Chemistiy			-		f		f	
Pregnancy test"								
C-SSRS								
Monti·eal Cognitive Assessment								
DaTscan (for idiopathic subjects)								
Revised Hamilton Rating Scale for Depression								
Subject enrolls in study		X						
Fasting blood-based glutathione cycle biomarkers								
Lumbar puncture (CNS biomarkers)								
Urine-based biomarkers								
MDS-UPDRS								
Timed motor tests (for subjects on dopaniine therapy)								
NMSS, PDQ-39, EQ-5D								
BDI,MADRS								
Dmg plasma concenti·ation°					c		c	
AE/SAE assessment	-	-	-			d	d	-
Concomitant medications assessment						d	d	-
Post-Treatment Assessments•								•

a. Screening values can be used if done w-ithin one month of baseline and if completed under fasted conditions

• Female subjects of childbea1mg potential must have a negative pregnancy test.

c. Full plasma concenti·ation profile will be obtained at Time= 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours aft.er dosing from the first IO subjects to complete I month of therapy at each site.12 hour PK can be obtained at time 0.

d. Month 2 assessments can be done by telephone. Any new AEs and associated concomitant medications repo1ted at Month 3 must be followed for 30 days; this follow up may be conducted by telephone.

e. AE/SAE and concomitant medication assessments conducted by telephone at least 10 days aft.er last dose. Additional assessments detenuined at Investigator discretion. SAEs are ti-acked from the time ICF is signed and all other AEs are ti·acked from the time first dose is administered;

f. TI1e baseline and **all subsequent laboratory assessments** should be obtained under fasting conditions.

A. Schedule of Dosing

	-2 to -1 Months		Day0		Month 1	Month2	Month3	Post-Treatment
Dosing Schedule	**Screening**	**Run-in (±30 days)**	**Baseline**		**Day29 (±3 days)**	**Day 57d (±3 days)**	**Day85 (±3 days)**	**Up to30 Days after Last Dose•**
EPI-589 500-mg BID								
Dispense Study Drug								
Dmg Reconciliation with diaries								

III. INTRODUCTION

A. Background Information and Rationale

Parkinson's disease (PD) is a highly morbid neurodegenerative movement disorder that has a number of neuromuscular, cognitive and neuropsychiatric manifestations as well as non-neurological symptoms. PD is the second most common neurodegenerative disorder with an estimated prevalence of 6.3 million people worldwide (EPDA).

PD has long been considered a non-genetic (idiopathic) disease; however, about 5% of patients have an identifiable mutation. Disease onset typically occurs after age 50, however, in a subset of patients, disease onset can occur at a younger age. The primary motor symptoms result from death of dopamine-producing cells in the pars compacta region of the substantia nigra. However, the mechanisms underlying this cell death and disease pathology remain poorly understood. There is no approved treatment for PD capable of modifying disease progression. Current therapies partially address disease motor symptoms through levodopa or dopamine agonists or other agents, and other disease symptoms (e.g. neuropsychiatric symptoms), but disability tends to increase over time despite these treatments.

The association of PD with mitochondrial pathology and high levels of oxidative stress are well established. Increased levels of oxidative stress have been consistently measured in post-mortem specimens from PD patients (Maarouf 2012, Reale 2012). The occurrence of PD-like symptoms in heroin addicts exposed to MPTP in the 1980s established a first link between PD and mitochondrial injury (Langston 1983, Dauer and Przedborski 2003). MPTP inhibits complex 1 of the mitochondrial respiratory chain and induces degeneration of dopaminergic cells through oxidative stress-mediated injury. The link between mitochondrial injury and PD was further strengthened by the induction of PD symptoms following exposure to another neurotoxic complex 1 inhibitor, rotenone (Betarbet et al 2000, Greenamyre et al. 2003), which like MPTP has come to be used in pre-clinical testing for its phenotypic similarities to PD.

Furthermore, the identification of genetic mutations such as PINK1, parkin, LRRK2 and others in mitochondrial genes in familial PD patients provided the strongest link between the mitochondria and PD (Winklhofer and Haass 2010). Normally these genes influence oxidative balance and provide neural protection of the dopaminergic neurons that are affected by PD. PINK1 and parkin are involved in protecting against oxidative stress (OS) and overabundant reactive oxygen species (ROS), and are implicated in cell morphology and dynamics, as well as in the preferential degradation of dysfunctional mitochondria or "mitophagy" (Ashrafi et al. 2014). Mutant LRRK2 leads to the accumulation of misfolding intracellular protein accumulations, cell stress and apoptosis (Giasson et al. 2006, Zhu et al. 2006).

The importance of oxidative stress in PD pathology is further substantiated by the measurement of decreased levels of reduced glutathione in the brains of patients with PD (Holmay et al. 2013). Glutathione levels are low at very early stages of PD and correlate with disease severity (Riederer et al. 1989), and experimental induction of glutathione depletion leads to mitochondrial complex I dysfunction (Jha et al, 2000;). Reduced glutathione is an essential intermediary

metabolite that serves as the primary native cellular antioxidant. In a state of high oxidative stress, elevated levels of ROS outstrip the supply of glutathione (GSH) resulting in depletion of GSH and ROS-mediated cell death.

Given the important role of oxidative stress and mitochondrial pathology in PD, a redox-active therapy that could target key pathways in cellular OS response pathways may hold promise for the treatment of PD.

B. Rationale for the Study of EPI-589 in Parkinson's Disease

EPI-589 is a redox active molecule that has demonstrated potency (EC50 <100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with idiopathic and familial PD genetic subtypes including PINK1, parkin and LRRK2.

In these cell-based assays, primary fibroblasts from patients (and control) were pre-incubated with and without test compound, then treated with L-buthionine-(S,R)-sulfoximine (BSO), a GSH synthesis inhibitor, to initiate depletion of cellular GSH. GSH depletion has been shown to lead to OS and disruption of calcium homeostasis resulting in loss of the mitochondrial membrane potential and cell death. Under these conditions, the control cells are resistant to the stress and the fibroblast cells from patients with disease indications die within 36 to 48 hours. Pretreatment of cells with EPI-589 prior to initiation of GSH depletion potently protected against oxidative stress-mediated cell death, with EC_{50} response concentrations of 16 to 52 nM. (Table 1).

Table 1: Cell Line Rescue with EPI-589 in Parkinson's Disease Genetic Subtypes

	EPI-589 **EC_{50} (nM range)**
PINK1	26-36
LRRK2	16-18
parkin	42-52

C. Name and Description of Investigational Product

The IUPAC name of 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 derived from resolved (R)-Trolox®, a derivative of vitamin E in the form of a pale yellow to yellow solid. The EPI-589 drug product will be provided in a 250-mg tablet formulation.

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. In 28-day and 91-day repeat-dose toxicity studies in rat and cynomolgus monkey, the no observed adverse effect level (NOAEL) was 300 mg/kg/day, corresponding to combined mean Cmax values of 37,717 to 56,500 ng/mL (rat) and 14,300 to 16,417 ng/mL (monkey), and a combined mean area under the plasma concentration-time curve from time zero to the last measurable concentration (AUClast) value of 149,495 to 297,000 ng.h/mL (rat) and 47,300 to 67,656 ng.h/mL (monkey) (Studies 1660-038, 1660-039, 1660-063, and 1660-064).

A phase 1 clinical study demonstrated that healthy subjects administered 500 mg EPI-589 BID for 14 days showed a mean Cmax value of 1,890 ng/mL and a mean AUClast value of 5,240 ng.h/mL (Study EPI589-14-01). These plasma concentrations are well below the mean exposure values in monkey associated with the NOAEL in the toxicity studies, corresponding to safety margins of approximately 7- to 8-fold for the mean Cmax and 9- to 12-fold for the mean AUC.

During the 28-day repeat-dose toxicity studies, rat and monkey were exposed to up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-039 and 1660-038). The NOAEL for both studies was 300 mg/kg/day. Rats exposed to 1,000 mg/kg/day exhibited adverse 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 showing corresponding microscopic pathology. The majority of these findings were resolved following the 28-day recovery period. Monkeys exposed to 1,000 mg/kg/day showed significant test-article related morbundity that resulted in half the animals in the high dose group being euthanized on Days 3 and 4 and the remaining animals being euthanized on Day 9. These animals exhibited significant elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values, and microscopic findings in the kidney, liver, skeletal muscle, heart, and lymphoid tissues. In several of the animals the primary cause of morbidity was determined to be test-article related renal tubular degeneration/necrosis.

During the 91-day repeat-dose toxicity studies, rat and monkey were exposed to up to 300 mg/kg/day EPI-589 PO (Studies 1660-063 and 1660-064). The NOAEL for the rat study was 300 mg/kg/day and the no observed effect level (NOEL) for the monkey study was 300 mg/kg/day. Male rats exposed to 300 mg/kg/day and [redacted] rats exposed to ≥ 100 mg/kg/day exhibited mild test-article related effects on hematology parameters consistent with hemolysis and bone marrow regeneration. These findings were not considered adverse.

Development and reproductive toxicology studies were conducted in rat and rabbit at doses up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-069, 1660-067, and 1660-068). The NOAEL for reproductive toxicity in rat was demonstrated to be 1,000 mg/kg/day (1660-069). The NOAEL

for developmental toxicity in rat and rabbit during the embryofetal studies was deemed to be 300 mg/kg/day (Studies 1660-067 and 1660-068). Rats exposed to 1,000 mg/kg/day exhibited 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. Rabbits exposed to 1,000 mg/kg/day exhibited 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 (Study EPI589-14-01) and rabbits exposed to 1,000 and 300 mg/kg/day EPI-589 is approximately 179- to 236-fold and 47- to 50-fold, respectively. 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 (Study AD58AS.502ICH.BTL); 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 (Study AD58AS.331ICH.BTL); and negative in the in vivo micronucleus assay in rat (Study AD58AS.125012ICH.BTL). These data indicate a low clinical mutagenicity risk.

Primary pharmacodynamics studies demonstrated that EPI-589 is a potent rescue agent in cellular models of diseases of energy metabolism and oxidative stress. In vitro cellular models utilizing primary human fibroblasts from patients with ALS, Parkinson's disease and other diseases characterized by high levels of oxidative stress, or striatal cells derived from mouse models of Huntingdon's disease were used to assess the potential of EPI-589 to mitigate the harmful effects of oxidative stress (Studies EPI-BA-000216, EPI-BA-000363, and EPI-BA-000362). Pretreatment of patient cells with EPI-589 potently protected against oxidative stress-mediated cell death in a concentration dependent manner. Furthermore, EPI-589 normalized 3-nitrosotyrosine (3NT) levels, a biomarker of oxidative stress, and increased glutathione levels in mouse striatal cells under oxidative stress conditions.

In secondary pharmacodynamics in vitro receptor/ion channel binding studies, EPI-589 did not significantly affect off-target molecular targets (Study EPI-BA-159). In safety pharmacology studies, EPI-589 did not significantly affect ion channel current in the hERG assay (Study 130719.FEK); did not affect ECG parameters during the 28-day and 3-month repeat-dose toxicology studies in monkey at doses up to 1,000 mg/kg/day (only Day 1 data collected for animals administered 1,000 mg/kg/day and up to Day 91 data collected for animals administered up to 300 mg/kg/day) (Studies 1660-038 and 1660-064); and did not change respiratory function or adversely impact neurobehavioral function in rat at doses up to 1,000 mg/kg (Studies 1660-051, 1660-050, and 1660-063).

In single dose exposure PK studies, EPI-589 was absorbed rapidly in rat, dog, and monkey, with mean T_{max} values ranging from .08 to 1 hour and mean T1/2 values ranging from 3.7 to 5.0 hours (Studies EPI-BA-53, EPI-BA-59, EPI-BA-72, and EPI-BA-302). EPI-589 does not significantly induce cytochrome P450 (CYP) enzymes and appears to be metabolized by reductases in the

liver cytosol and microsomal subcellular fractions and to a lesser extent by the family of CYP enzymes (Studies MC12M-0037 and MC14M-0018).

EPI-589 exhibited weak direct inhibition of CYP2B6, CYP2C8, CYP2C9, and CYP3A4/5 (both midazolam and testosterone as probe substrates) with estimated IC_{50} (μM) values and R values based on free plasma concentrations (shown in parentheses) of 28 (1.25), 40 (1.18), 92 (1.08), 34 (1.21), and 53 (1.13), respectively (Study MC14M-0020)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.

D2. Clinical Studies

Phase I Study EPI589-13-022 evaluated the pharmacokinetics, safety and tolerability of single ascending oral doses (SADs) of EPI-589 in healthy subjects and a preliminary evaluation of safety and tolerability data was performed. Sixteen AEs were reported in the 36 subjects who received administration of EPI-589. Ten subjects (27.8%) who received EPI-589 (and 2 subjects, 20% on placebo) reported AEs that were assessed as related. All were mild and resolved during the study, with the exception of a common cold (1 subject) and cold sore (1 subject). 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. Twenty-six subjects (65.0%) on EPI-589, and 8 subjects (80%) on placebo reported AEs. Twenty-four of 34 AEs were considered by the Investigator to be related to EPI-589. Nineteen subjects (47.5%) on EPI-589, and 6 subjects (60%) on placebo reported AEs that were assessed as related. All adverse events were mild, except for 1 AE which was moderate (unrelated brain contusion). All AEs were resolved during the study, with the exception of one, which was a common cold. 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 the MAD study it may be concluded that there is no objection to proceed with treatment with 250-mg, or 500-mg doses of EPI-589.

E. Human Pharmacokinetics

EPI-589 was fast absorbed following oral administration in SAD Study EPI589-13-022. The median C_{max} was attained approximately within 1 hour under fasted conditions after dosing. The median T_{max} values were attained in 0.50 to 1.00 hours over the dose range of 50 to 1000 mg under fasted conditions and 3.01 hours at the 500 mg dose level under fed conditions. Mean half-life ranged from 5.55 to 10.7 hours over the dose range of 50 to 1000 mg under fasted conditions and 4.91 hours at the 500 mg dose level under fed conditions. Half-life was independent of the dose levels over the dose range of 50 to 1000 mg under fasted conditions. The rate of EPI-589 absorption, as measured by C_{max}, was decreased by 24.07% under fed conditions at the 500 mg

dose level. The extent of absorption as measured by AUCs (AUC_{0-t} or AUC_{0-inf}) was not affected under fed conditions in the 500 mg dose groups.

In MAD study EPI589-14-01, 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 of various ages and smoking status. No significant effects of age or smoking on EPI-589 pharmacokinetics were observed in this study. Dose proportionality existed in the exposures (AUC_{0-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

EPI589-15-002: A Phase 2A Safety and Biomarker Study of EPI-589 in in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects.

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 meals.

H. Compliance Statement

This study will be conducted in full accordance with all applicable research policies and procedures, the EU Clinical Trials Directive, all applicable EU and 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, will obtain consent and will 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.

I. Relevant Literature and Data

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

IV. STUDY OBJECTIVES

A. Primary Objective

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 PD.

B. Secondary Objectives

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

1. Glutathione cycle biomarkers as measured in blood, cerebral spinal fluid, and urine
2. Clinical disease state as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D
4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA)
5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery & Asberg Depression rating scale (MADRS)
6. Pharmacokinetics
7. Hematology, blood chemistry, electrocardiogram

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V. INVESTIGATIONAL PLAN

A. General Schema of Study Design

Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues.

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects. Given that the investigational drug targets an enzyme key to glutathione synthesis and that glutathione depletion has been found to be associated with PD, we are seeking to determine the safety and potential biochemical benefit of EPI-589 in PD subjects as assessed by glutathione cycle biomarkers. If we determine that there are a subset of idiopathic PD patients—whether due to disease stage or baseline biomarker profile—who are more likely to be EPI-589 responsive, we will seek to enroll additional numbers of these subjects in the adaptive phase so that we can increase the number of likely biomarker responsive subjects. EPI-589 will be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues.

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 run-in scans, CNS, blood-based biomarker, urine-based biomarker and clinical measurements will be collected.

A3. Baseline

Baseline assessments, scans, blood-based biomarker, urine biomarker, 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-based biomarker, urine biomarker, and clinical measurements will be collected at Day 29 (± 3 days) and Day 85 (± 3 days).

A5. End of Treatment

End of treatment data will be collected at the last study visit Day 85 (± 3 days).

AEs reported as ongoing at Day 85 (± 3 days) and/or any concomitant medications associated with such events 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.

A6. Post-Treatment Follow-up

Post-Treatment Follow-up will be at least 10 days and up to 30 days after last dose: AE/SAE and concomitant medication assessments conducted by telephone. Additional assessments to be determined at Investigator discretion.

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 biomarker and clinical baseline measurements. EPI-589 will then be administered for 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues. A post-treatment follow-up will be conducted at least 10 days and up to 30 days after last dose.

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

This study will be conducted at five study sites:

- [redacted], UK
- [redacted], USA.
- [redacted] Germany
- [redacted] USA
- [redacted] USA

Approximately 40 subjects with PD are projected:

- 20 with genetically-defined subtypes
- 20 PD idiopathic PD

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the same study protocol and outcome metrics.

D. Study Population

D1. Inclusion Criteria

1. Hoehn and Yahr stage ≤ 3.0
2. Ambulatory with or without assistance
3. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., hormonal methods, including oral, subcutaneous, and intrauterine; barrier methods, including [redacted] condom, [redacted] condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study treatment.
4. Willingness and ability to comply with study procedures
5. If on medications for PD drugs, then medication regimen must be stable for 60 days prior to enrollment
6. Abstention from use of other investigative or non-approved drugs for the duration of the trial

For Idiopathic Subjects

7. A diagnosis of idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit
8. Age 40 to 75 years
9. Within 5 years of diagnosis of Parkinson's disease

For Genetic Subtype Subjects

10. A confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LRKK2 or other mitochondrial genetic subtype
11. Age 21 to 75 years

D2. Exclusion Criteria

1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation
2. Use of antioxidant supplements, specifically vitamins E and C beyond the recommended daily allowance
3. Other Parkinsonian disorders
4. MoCA score of <24
5. Revised Hamilton Rating Scale for Depression ≥ 11
6. Parkinsonism due to drugs or toxins
7. Diagnosis of any other clinically significant neurologic disease that will confound the assessment of effect of study drug on disease progression
8. Malignancy within past two years
9. Pregnant or plans to become pregnant or breast feeding
10. History of stroke
11. History of brain surgery
12. Hepatic insufficiency with liver function tests (LFTs) > 3 times upper limit of normal

13. Renal insufficiency as defined by creatinine > 1.5 times normal
14. End stage cardiac failure
15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD

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VI. STUDY PROCEDURES

A. Screening Visit

Screening evaluations will be performed within two months of first dose. The Investigator will inform each prospective subject of the nature of the study, explain the potential risks, and must 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. Receipt and review of previous testing including genetic tests
4. Physical examination including vital signs
5. Height and weight
6. 12-lead ECG
7. Laboratory assessments for hematology, coagulation, and serum chemistry (See Sections VII.D3.a and VII.D3.b)
8. Urine pregnancy test (women of childbearing potential must have a negative urine pregnancy test; see Section VII.D3.c)
9. MDS-UPDRS
10. MoCA
11. DaTscan (for idiopathic subjects only)
12. Revised Hamilton Rating Scale for Depression
13. AE/SAE assessments
14. Concomitant medications assessment (last 60 days prior to enrollment)

A1. Run-in Assessments

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 within one month for Run-in assessments. These will 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. Blood-based glutathione cycle biomarkers
2. CNS biomarkers (lumbar puncture)
3. Urine biomarkers
4. Timed motor tests (for subjects on dopamine therapy)
5. AE/SAE assessments
6. Concomitant medications review

B. Treatment Phase

After the Run-in phase, the subject must return to the clinic within 30 days (± 3 days) for baseline assessments. In-clinic study visits are scheduled at Month 1 and Month 3. The Month 2 study assessments can be conducted via telephone. End of treatment assessments will be

conducted 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 including vital signs
2. Height and weight*
3. 12-Lead ECG*
4. Blood-based GSH cycle biomarkers
5. Urine-based biomarkers
6. Laboratory assessments for hematology, coagulation and serum chemistry*
7. Urine pregnancy test ([redacted] of child bearing potential)
8. C-SSRS (Columbia Suicide Severity Rating Scale)
9. MDS-UPDRS
10. NMSS, PDQ-39, EQ-5D
11. BDI, MADRS
12. Timed motor tests (for subjects on dopamine therapy)
13. AE/SAE assessments
14. Concomitant medications review

* Screening results for these assessments may be used if obtained within 1 month of Baseline and if they are completed under fasted conditions.

B2. Study Visit Assessments

- Month 1 Clinic Visit (Day 29 ± 3 days):

The following will be assessed or performed at the Month 1 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry
5. Urine pregnancy test ([redacted] of child bearing potential)
6. C-SSRS
7. Blood-based GSH cycle biomarkers
8. Urine-based biomarkers
9. MDS-UPDRS
10. Pharmacokinetics**: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.
11. AE/SAE assessments
12. Concomitant medications review

- Month 2 Visit (Day 57 ± 3 days)

Month 2 assessments can be conducted by telephone and must include review of:

1. AE/SAE assessments
2. Concomitant medication

- Month 3 Clinic Visit (Day 85 ± 3 days)

The following will be assessed or performed at the Month 3 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry
5. Urine pregnancy test ([redacted] of child bearing potential)
6. C-SSRS
7. Blood-based GSH cycle biomarkers
8. Urine-based biomarkers
9. CNS biomarkers
10. MDS-UPDRS
11. Pharmacokinetics**: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.
12. AE/SAE assessments
13. Concomitant medications review
14. MoCA
15. NMSS, PDQ-39, EQ-5D
16. BDI, MADRS
17. Timed motor tests (for subjects on dopamine therapy)

*B3. Pharmacokinetics***

Plasma concentration samples will be collected from the first 10 subjects to complete 1 month of therapy at each site, at the following time points:

- Month 1 (Day 29 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose
- Month 3 (Day 85 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose

** 12 hour PK can be obtained at time 0

B4. Early Termination Study Visit

Subjects who terminate from the study after receiving first dose and prior to the completion of all scheduled visits should have the end of treatment visit assessments completed as soon as possible.

C. End of Treatment Visit

End of treatment visit takes place at Month 3 (Day 85 ± 3 days) and includes the assessments listed in Section VB2 Study Visit Assessments.

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. Post-Treatment Follow-up

Post-Treatment Follow-up will be at least 10 days and up to 30 days after last dose, with AE/SAE and concomitant medication assessments conducted by telephone. Additional assessments to be determined at Investigator discretion.

E. Unscheduled Visits

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

F. Concomitant Medication

Any medication taken by a subject ≤ 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 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 consulting the Investigator.

G. 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 and for the duration of the study in a trial of a device, drug or other therapy for PD

H. Subject Withdrawals

Subjects receive study treatment until treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The following conditions require subject discontinuation from all study treatment:

1. At their own request or at the request of their legally authorized representative

2. If a subject experiences an adverse event that is deemed related to treatment with EPI-589 and in the Investigator's or the Sponsor's medical judgment continuation of treatment would be detrimental to the subject.
3. At the specific request of a regulatory agency for termination of treatment of an individual subject or all subjects under the protocol
4. Subject participation in another clinical study using an investigational agent or investigational medical device
5. Use of prohibited medications such as vitamins E and C beyond the recommended daily allowance.
6. Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use medically accepted methods of contraception
7. If a subject becomes pregnant.
8. Significant noncompliance with the protocol in the opinion of the Investigator or the Sponsor

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 should 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 PD.

B. Secondary Endpoints (Efficacy)

1. Blood-based biomarkers
2. CNS-based biomarkers
3. Urine-based biomarkers
4. MDS-UPDRS
5. NMSS
6. PDQ-39
7. EQ-5D
8. MoCA
9. BDI
10. MADRS
11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)
12. Pharmacokinetics

C. Secondary Endpoints (Safety)

1. Routine assessments of AEs and SAEs
2. Dose limiting toxicities
3. Routine serum chemistries with liver function tests
4. C-SSRS
5. Routine hematology tests with coagulation tests
6. Electrocardiogram

D. Screening and Baseline Evaluation

D1. Physical Examination

Complete physical exams will be conducted (excluding genital/rectal exam) at protocol specified study visits. 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, heart, abdomen, and extremities.

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).

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

D2. Height and Weight

Weight (kg) will be measured in ordinary indoor clothing (i.e., street clothes, scrubs, etc.) with shoes off. Height will be recorded in centimeters (cm).

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.

D3. Laboratory Evaluations

Subjects 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 I).

a. Hematology

a. Erythrocytes: red blood cell (RBC) count, hematocrit, hemoglobin, , mean corpuscular volume (MCV)
b. Leukocytes: white blood cell count (WBC) and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)
c. Platelets: platelet count
d. Coagulation: prothrombin time (PT) with INR, and partial thromboplastin time (PTT)

b. Serum chemistry

a. Liver: Alkaline Phosphatase (ALP), ALT (serum glutamic-pyruvic transaminase [SGPT]), AST (serum glutamic-oxaloacetic transaminase [SGOT]), bilirubin (total and direct), gamma-glutamyl transferase (GGT), and lactic dehydrogenase (LDH)
b. Renal: blood urea nitrogen (BUN), and creatinine
c. Electrolytes: sodium, potassium, chloride and carbon dioxide (CO_2)
d. General: creatine phosphokinase (CPK), total protein, albumin, calcium, magnesium, glucose, phosphate
e. Lipids: cholesterol (total), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL), cholesterol, and triglycerides

c. Urine pregnancy test

1. Human chorionic gonadotropin (HCG) beta subunit will be measured on all [redacted] subjects of childbearing potential.

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.

Diagnoses associated with any NIH Common Terminology Criteria for Adverse Events (CTC v4.03) Grade 3 or 4 laboratory abnormalities will be recorded as adverse events (AEs**)** on the CRF. The recorded event 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.

D4. 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.

E. Sample Collection Procedures, Bioanalytical Methods and Sample Shipment

Subject samples will be identified by unique sample codes.

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

F. Efficacy Evaluations

F1. Glutathione Cycle Biomarkers

Blood, urine, and CNS levels of oxidized and reduced GSH as well as GSH metabolites will be used to evaluate EPI-589 target engagement and ability to correct a key biochemical aspect of disease pathology.

F2. Parkinson's Disease Rating (MDS-UPDRS)

The MDS-UPDRS is a tool for monitoring the impact of PD, the degree of disability caused, and complications from treatment. Part I evaluates nonmotor experiences of daily living; Part II evaluates motor experiences of daily living; Part III is a motor examination and includes the Hoehn and Yahr scale; Part IV examines motor complications (e.g., motor fluctuations and dyskinesias).

Several questions from Part I and all questions from Part II are designed to be amenable to a patient/caregiver questionnaire format; the remaining interview (Part I and Part III) and examination (Part IV) are designed with the expectation they can be completed within 30 minutes. Each item is measured on a five-point scale.

F3. Non-motor Symptoms (NMSS)

Non-motor symptoms are evaluated using the NMSS which is divided into 30 questions in 9 different domains including such symptoms as dribbling saliva, constipation, depression, sleep disorders, apathy, hallucinations and dementia. Symptoms are quantified based on their severity (using a scale of 0 to 3) and frequency (using a scale of 0 to 4). The final cumulative scores are derived from adding up the product of the frequency score times severity score for each of the 30 questions.

F4. Parkinson's Disease Questionnaire (PDQ-39)

PDQ-39 is a self-administered questionnaire for patients with PD that has 39 questions relating to eight key areas of health and daily activities, including both motor and non-motor symptoms. It is scored on a scale of 0 to 100, with lower scores indicating better health, and high scores more severe symptoms.

F5. EQ-5D

EQ-5D is a questionnaire designed to provide measures of health-related quality of life states, consisting in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

F6. Montreal Cognitive Assessment (MoCA)

MoCA is a 30-point questionnaire for cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Severity ranges are approximately: 26 to 30 normal; 18 to 26 mild cognitive impairment; 10-17 moderate cognitive impairment; < 10 severe cognitive impairment.

F7. Beck Depression Inventory (BDI)

The BDI is a self-reporting inventory that measures characteristic attitudes and symptoms of depression, including physical symptoms. Twenty-one questions have four responses each (rated 0 to 3) with a total cumulative score scale ranging from 1-10 considered normal) > 40 (extreme depression).

F8. Montgomery and Asberg Depression rating scale (MADRS)

The MADRS is a clinician-rated tool for measuring changes in depressive symptom severity. Ten core symptoms and cognitive features are rated on a severity scale of 0 to 6. Higher scores indicate increasing depressive symptoms.

F9. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)

Timed motor tests are simple, objective, quantitative measures for the assessment of Parkinson's disease. They include, in an on-medication and an off-medication state, timed recorded physical movements.

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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.

A1. Analysis Populations

Demographic characteristics and baseline efficacy data will be presented and summarized by treatment group for all subjects in the efficacy intent to treat (EITT) population. Demographic information will also be summarized by treatment group 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. CNS biomarkers
3. Urine-based biomarkers
4. MDS-UPDRS
5. NMSS
6. PDQ-39
7. EQ-5D
8. MoCA
9. BDI
10. MADRS
11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)
12. Pharmacokinetics

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 PD.

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 40 subjects (20 with genetically-defined subtypes of PD and 20 idiopathic PD subjects). Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker-responsive idiopathic PD subjects to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the same study protocol and outcome metrics.

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IX. STUDY MEDICATION

A. Description

EPI-589 is presented as an immediate release film-coated tablet. Each tablet contains 250 mg of EPI-589 and the following compendial excipients: lactose, 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, in compliance with 21 CFR 312.6 and Eudralex Vol. 4 EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13

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 HPDE 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]).

C. 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 verification with subject-completed diary cards and returned used drug supply.

D. Drug Accountability

Dosing information will be captured on a subject Dosing Diary Form. This form is part of the 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 Investigator study file to assure the study medication is 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 either be 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 in accordance with the IRB policies and as detailed below. AEs that are not serious will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

B1. Safety Guidance

Based on the known clinical manifestations of Parkinson's disease, we expect that many AEs could occur during the course of the trial that are well documented to occur as the results of the natural history of this disease. These include, but are not limited to worsening neuromuscular function, depression, decline in cognitive function, loss of vision and other ophthalmological symptoms, loss of coordination and loss of speech.

As there are no data available regarding EPI-589 phototoxicity, investigators are to advise subjects to take measures to minimize exposure to ultraviolet (UV) light for the duration of the study and for one week after the last dose.

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 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" or "AE".

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)

An 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; or
5. A congenital anomaly/birth defect.

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 subject 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 an SAE which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether other AEs, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject, require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

[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; follow-up of the pregnancy, fetus, and child will continue for at least 8 weeks after delivery. While pregnancy itself is not considered an

AE or SAE, all pregnancies should be reported using the same process as for SAEs. Any pregnancy complications or an outcome other than a healthy, normal outcome will be recorded as an AE or SAE.

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.

C3. Non-serious Adverse Event

A non-serious AE 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 and reappears with re-introduction 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 indicated.

Grade 2 – Moderate limitation in activity, some assistance may be needed; minimal noninvasive medical intervention/therapy indicated.

Grade 3 – Severe limitation in activity, assistance usually required; medical intervention/therapy required; hospitalization or prolongation of hospitalization indicated; disabling.

Grade 4 – Extreme limitation in activity, significant assistance required; urgent medical intervention/therapy required; life-threatening consequences.

Grade 5 – Death

C6. Definition of Unexpected Adverse Event

Any AE, the specificity or severity of which is not consistent with those listed in the current investigator's brochure is considered "unexpected."

C7. Notification of SAEs

The Investigator is responsible for promptly notifying the IRB/IEC of all study on-site SAEs 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 MedWatch or CIOMs form (as appropriate).

SAEs (whether unexpected or expected AEs) must be documented on the designated SAE form. The SAE must be reported to the medical expert and appropriate BioElectron Technology Corporation BioElectron-assigned pharmacovigilance staff within 24 hours, according to regulatory, Sponsor, or ICH-E6 Good Clinical Practice, followed by the SAE form within two 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 Investigator and/or Medical Expert must also inform the Study Monitor and the Sponsor in all cases. Any SAEs must also be reported to the IRB/IEC. The Sponsor or designee will ensure that all legal reporting requirements are met.

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 a follow-up SAE forms.

The instructions to sites for the completion of SAE reports give detailed guidance on the reporting of SAEs and AEs initially reported as non-serious that become serious. When a non-serious event becomes serious, details must be forwarded immediately to the Medical expert and BioElectron Technology Corporation or BioElectron-assigned 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 reported to the relevant competent authorities.

In the US, all fatal or life-threatening suspected unexpected serious adverse events assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA as soon as possible (i.e., by telephone or facsimile transmission), but no later than 7 calendar days after first knowledge by the Sponsor that a report qualifies as a suspected unexpected fatal or life-threatening reaction. All unexpected serious adverse events, other than fatal or life-threatening, assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA within 15 calendar days from the day the Sponsor determines that the information qualifies as a SUSAR.

In the UK, the Sponsor or trial investigator must act immediately or at least within 24 hours after becoming aware of a SUSAR by informing the MHRA's Clinical Trial Unit by telephone. The MHRA must then be informed in writing within 3 days of the incident. All SUSARs originating in the UK or originating outside the UK involving the same medicinal product are to be reported. Fatal or life-threatening SUSARs are to be reported as soon as possible, but no later than after 7 days. Any additional relevant information must be sent within 8 days of the report. Non-fatal or non-life-threatening SUSARs are to be reported as soon as possible but no later than 15 days after becoming aware of the reaction.

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. All SAEs should be followed until either resolved or stable.

C9. Dose Modification Guidelines

In the event that any patient develops elevated INR ≥ grade 2 in severity (> 1.5-2.5 x ULN) per CTCAE criteria version 4.0 thought to be related to treatment with EPI-743, administration of EPI-589 will be reduced by 1/2 to 50 percent of the starting dose. Should the INR toxicity not resolve to at least grade 1 in severity within two weeks of the initial dose reduction, administration of EPI-589 may either be further reduced or discontinued.

Once a patient's dose is reduced due to elevated INR thought to be related to study drug administration, their dose should not be re-escalated.

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 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.

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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 (0.001%), a systematic review of the database will be undertaken and corrections will be made to achieve an error rate of less than 0.001%.

AEs will be coded using MedDRA, version (14.3). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary, March 2014.

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 or 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, and the General Data Protection Regulation (GDPR).

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 EPI-589-14-01 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 PD. Therefore, we cannot assure that subjects will benefit from treatment with EPI-589. Potential benefits may manifest in a variety of ways, such as in disease-related parameters, functioning, and quality of life.

G3. Risk-Benefit Assessment

There are no effective and/or approved disease modifying treatments available for PD, 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 hold benefit for patients with PD. This is the first study to better understand EPI-589 target engagement and potential therapeutic

benefit in subjects with PD. 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.

This Study is part of a multicenter clinical research study. Accordingly, 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 while this Study is being conducted at other center/s. Only after the completion of this Study at all other centers, provision of the data to the FDA or EMA for review and comment, and publishing the combined data from all of the centers, may the Principal Investigator 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.

XIII. LIST OF ABBREVIATIONS

AE	adverse event
AI	accumulation index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AR	accumulation ratio
BDI	Beck Depression Inventory
BID	twice daily
BSO	L-buthionine-(S,R)-sulfoximine
C-SSRS	Columbia-Suicide Severity Rating Scale
CBC	complete blood count
CFR	Code of Federal Regulations
CK	creatinine kinase
CNS	central nervous system
CoQ10	Coenzyme Q 10
CRF	Case Report Form
CRO	Contract Research Organization
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DaT	dopamine transporters
DSMB	data safety monitoring board
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EITT	efficacy intent-to-treat
EPDA	European Parkinson's Disease Association
EU	European Union
%F	percent fluctuation
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GCRC	good clinical research practice
GDPR	General Data Protection Regulation
GSH	glutathione
GSSG	glutathione disulfide
HDPE	high density polyethylene
hERG	human Ether-a-go-go Related Gene
HCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HMPAO	hexamethylpropylene amine oxime
ICF	informed consent form
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUPAC	International Union of Pure and Applied Chemistry

kg	kilogram
Λz	apparent terminal constant
LFT	liver function test
MAD	multiple ascending (oral) dose
MADRS	Montgomery and Asberg Depression rating scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
mg	milligram
mL	milliliter
MoCA	Montreal Cognitive Assessment
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPV	mean platelet volume
mtDNA	mitochondrial DNA
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NF	National Formulary
nM	nanomolar
NMSS	Non-motor Symptoms Scale
NOAEL	no observed adverse effect level
NQ01	NAD(P)H Quinone oxidoreductase 1
OD	once daily
OTC	over-the-counter
PD	Parkinson’s disease
PDQ-39	39-Item Parkinson’s Disease Questionnaire
PO	by mouth
PT	Prothrombin Time
PTT	Partial Prothrombin 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
SAD	single ascending (oral) dose
SAE	serious adverse event
SD	standard deviation
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
UV	ultraviolet

XIV. SIGNATURE OF SPONSOR

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: 11 R.l:i 2ol 7 Signature: [redacted]

[redacted]
350 North Bernardo Ave
Mountain View, CA 94043

XV. REFERENCES

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Summary of Changes
Amendment 4.0
EPI589-15-002

A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects

Protocol Number	EPI589-15-002
Original Protocol Date	27 April 2015
Amendment 1.0 Date	09 September 2015
Amendment 2.0 Date	04 January 2016
Amendment 3.0 Date	10 October 2016
Amendment 4.0 Date	17 February 2017
Study Sponsor	BioElectron Technology Corporation 350 North Bernardo Avenue Mountain View, CA 94043
Sponsor's Representative	[redacted] BioElectron Technology Corporation 350 North Bernardo Avenue Mountain View, CA 94043

KEY CHANGES TO THE PROTOCOL

Amendment 4.0 provides the following change and rationale:

Change	Rationale
• Change in Company Name from Edison Pharmaceuticals to BioElectron Technology Corporation	• Edison Pharmaceuticals, Inc. has changed its name to reflect our broader mission and business applications.

End of Document

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EPI589-15-002
A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects

Original Protocol:	27 April 2015
Protocol Amendment 1.0:	09 September 2015
Protocol Amendment 2.0:	04 January 2016
Protocol Amendment 3.0:	10 October 2016

Edison Pharmaceuticals, Inc.
350 North Bernardo Avenue
Mountain View, CA 94043

Table of Contents

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I. PROTOCOL SYNOPSIS

Title of study	A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects
Protocol number	EPI589-15-002
IND number	126,795
EudraCT number	2015-001786-10
Original Protocol	27 April 2015
Protocol Amendment 1.0	09 September 2015
Protocol Amendment 2.0	04 January 2016
Protocol Amendment 3.0	03 October 2016
Investigative Drug	EPI-589
Study Sponsor	Edison Pharmaceuticals Inc. 350 North Bernardo Avenue Mountain View, CA 94043
Investigators and Investigative Sites	• [redacted] Germany • [redacted] UK • [redacted] USA • [redacted] USA • [redacted] USA
Study population	Approximately 40 subjects with Parkinson's disease (PD) including 20 subjects with genetically-defined subtypes

Rationale for Study

Mitochondrial pathophysiology

It is now well appreciated that defects in mitochondrial function contribute to the pathophysiology of PD both in subjects with defined genetic defects as well as those with idiopathic forms of the disease.

High morbidity

Despite the available therapies for symptomatic relief, PD remains a highly morbid disease. There are no approved treatments for PD capable of modifying disease progression.

Pre-clinical efficacy data

EPI-589 is a redox active molecule that has demonstrated potency (EC50 < 100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with idiopathic and familial PD subtypes including PINK1, parkin and LRRK2.

Study objectives

Primary Objective

To evaluate the effects of EPI-589 on safety as assessed by occurrence of drug-related serious adverse events in subjects with PD.

Secondary Objectives

To evaluate the effects of EPI-589 in subjects with PD on:

1. Glutathione cycle biomarkers as measured in blood, cerebral spinal fluid, and urine
2. Clinical disease state as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D
4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA) and
5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery and Asberg Depression rating scale (MADRS)
6. Pharmacokinetics
7. Hematology, blood chemistry, electrocardiogram

Study design	Open-label study with 30-day run-in phase.
Planned number of subjects	Approximately 40 subjects (20 with genetically-defined subtypes of PD and 20 idiopathic PD subjects). (Adaptive design component allows enrollment of up to 20 additional subjects with idiopathic PD to try to achieve a total of 20 subjects that have a biomarker response to EPI-589.)
Study duration	3 months (85 days ± 3 days) of study treatment preceded by a 1-month baseline parameter run-in period.
Test product, mode of administration, and dose	Test product EPI-589 in a tablet formulation at a strength of 250 mg Mode of Administration Oral with meal Dose EPI-589 500-mg BID
Reference therapy, dose, and mode of administration	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 (all subjects)	1. Hoehn and Yahr stage ≤ 3.0 2. Ambulatory with or without assistance 3. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., hormonal methods, including oral, subcutaneous, and intrauterine; barrier methods, including [redacted] condom, [redacted] condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study treatment. 4. Willingness and ability to comply with study procedures

5. If on medications and supplements for PD, then regimen must be stable for 60 days prior to enrollment
6. Abstention from use of other investigative or non-approved drugs for the duration of the trial

For Idiopathic Subjects

7. A diagnosis of idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit
8. Age 40 to 75 years
9. Within 5 years of diagnosis of Parkinson's disease

For Genetic Subtype Subjects

10. A confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LRRK2 or other mitochondrial genetic subtype
11. Age 21 to 75 years

Exclusion criteria

1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation
2. Vitamins E and C beyond the recommended daily allowance
3. Other Parkinsonian disorders
4. MoCA score of <24
5. Revised Hamilton Rating Scale for Depression ≥ 11
6. Parkinsonism due to drugs or toxins
7. Diagnosis of any other clinically significant neurologic disease that will confound the assessment of effect of study drug on disease progression
8. Malignancy within past two years
9. Pregnant or plans to become pregnant or breast feeding
10. History of stroke
11. History of brain surgery
12. Hepatic insufficiency with liver function tests (LFTs) > 3 times upper limit of normal
13. Renal insufficiency as defined by creatinine > 1.5 times normal
14. End stage cardiac failure
15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD

Treatment	Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues. Post-treatment follow-up will be at least 10 days and up to 30 days after last dose.
Efficacy variables	1. Blood-based glutathione biomarkers 2. CNS biomarkers 3. Urine-based biomarkers 4. MDS-UPDRS 5. Non-motor Symptoms Scale (NMSS) 6. PDQ-39 7. EQ-5D 8. MoCA 9. Beck Depression Inventory (BDI) 10. Montgomery & Asberg Depression rating scale (MADRS) 11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy) 12. Pharmacokinetics
Safety variables	<u>Clinical</u> 1. Routine assessments of AEs and SAEs 2. Dose limiting toxicities 3. Electrocardiogram 4. C-SSRS 5. Laboratory 6. Routine serum chemistries with liver function tests 7. Routine hematology tests with coagulation tests
Statistical Considerations	<u>Data Analysis</u> This is a within-subject, controlled open-label study seeking to determine the safety and tolerability of EPI-589 in patients with PD as well as to determine if EPI-589 can alter the biochemical signature of PD as assessed by peripheral blood biomarkers, CNS biomarkers, brain imaging biomarkers, and urine biomarker analysis. In addition, data on a number of disease-relevant clinical measures will be collected.

II. SCHEDULE OF ASSESSMENTS AND DOSING SCHEDULE

Tests	-2 to -1 Months		DayO		Month 1	Month 2	Month3 End of Treatment Visit	Post-Treatment Follow-up
	Screening	Run-in (upto 30 days from screenin2)	Baseline (27-33 days from run-in)		Day29 (± 3 days)	Day 57d (±3 days)	Day85 (±3 days)	Up to 30Days afte1·Last Dose•
Informed consent				Day 1 First Dose				
Inclusion/Exclusion criteria								
Past Medical history								
Pre:wous genetic testing review								
Physical exam & Vital signs								
Height & weight			•					
12-lead ECG			•					
Hematology (including coagulation panel)			•		f		f	
Semm Chemistiy			•		f		f	
Pregnancy test"								
C-SSRS								
Monti·eal Cognitive Assessment								
DaTscan (for idiopathic subjects)								
Revised Hamilton Rating Scale for Depression								
Subject enrolls in study		X						
Fasting blood-based glutathione cycle biomarkers								
Lumbar puncture (CNS biomarkers)								
Urine-based biomarkers								
MDS-UPDRS								
Timed motor tests (for subjects on dopamine therapy)								
NMSS, PDQ-39, EQ-5D								
BDI,MADRS								
Dmg plasma concenti·ation°					c		c	
AE/SAE assessment	•	•	•		•	d,•	d,e	•
Concomitant medications assessment						d	d	•
Post-Treatment Assessments•								•

a. Screening values can be used if done w-ithin one month of baseline and if completed under fasted conditions

• Female subjects of childbea1mg potential must have a negative pregnancy test.

c. Full plasma concenti·ation profile w-ill be obtained at Time= 0, and 0.5, I, 2, 4, 6, 8, and 12 hours after dosing from the first 10 subjects to complete I month of therapy at each site. 12 hotu·PK can be obtained at time 0.

d. Month 2 assessments can be done by telephone. Any new AEs and associated concomitant medications reported at Month 3 must be followed for 30 days; this follow up may be conducted by telephone.

e. AE/SAE and concomitant medication assessments conducted by telephone at least 10 days after last dose. Additional assessments detenuined at Investigator discretion. SAEs are ti·acked from the time ICF is signed and all other AEs are ti-acked from the time first dose is administered;

f. TI1e baseline and **all subsequent laboratory assessments** should be obtained under fasting conditions.

A. Schedule of Dosing

	-2 to -1 Months		Day0		Month 1	Month2	Month3	Post-Treatment
Dosing Schedule	**Screening**	**Run-in (±30 days)**	**Baseline**		**Day29 (±3 days)**	**Day 57d (±3 days)**	**Day85 (±3 days)**	**Up to30 Days after Last Dose•**
EPI-589 500-mg BID								
Dispense Study Drug								
Dmg Reconciliation with diaries								

III. INTRODUCTION

A. Background Information and Rationale

Parkinson's disease (PD) is a highly morbid neurodegenerative movement disorder that has a number of neuromuscular, cognitive and neuropsychiatric manifestations as well as non-neurological symptoms. PD is the second most common neurodegenerative disorder with an estimated prevalence of 6.3 million people worldwide (EPDA).

PD has long been considered a non-genetic (idiopathic) disease; however, about 5% of patients have an identifiable mutation. Disease onset typically occurs after age 50, however, in a subset of patients, disease onset can occur at a younger age. The primary motor symptoms result from death of dopamine-producing cells in the pars compacta region of the substantia nigra. However, the mechanisms underlying this cell death and disease pathology remain poorly understood. There is no approved treatment for PD capable of modifying disease progression. Current therapies partially address disease motor symptoms through levodopa or dopamine agonists or other agents, and other disease symptoms (e.g. neuropsychiatric symptoms), but disability tends to increase over time despite these treatments.

The association of PD with mitochondrial pathology and high levels of oxidative stress are well established. Increased levels of oxidative stress have been consistently measured in post-mortem specimens from PD patients (Maarouf 2012, Reale 2012). The occurrence of PD-like symptoms in heroin addicts exposed to MPTP in the 1980s established a first link between PD and mitochondrial injury (Langston 1983, Dauer and Przedborski 2003). MPTP inhibits complex 1 of the mitochondrial respiratory chain and induces degeneration of dopaminergic cells through oxidative stress-mediated injury. The link between mitochondrial injury and PD was further strengthened by the induction of PD symptoms following exposure to another neurotoxic complex 1 inhibitor, rotenone (Betarbet et al 2000, Greenamyre et al. 2003), which like MPTP has come to be used in pre-clinical testing for its phenotypic similarities to PD.

Furthermore, the identification of genetic mutations such as PINK1, parkin, LRRK2 and others in mitochondrial genes in familial PD patients provided the strongest link between the mitochondria and PD (Winklhofer and Haass 2010). Normally these genes influence oxidative balance and provide neural protection of the dopaminergic neurons that are affected by PD. PINK1 and parkin are involved in protecting against oxidative stress (OS) and overabundant reactive oxygen species (ROS), and are implicated in cell morphology and dynamics, as well as in the preferential degradation of dysfunctional mitochondria or "mitophagy" (Ashrafi et al. 2014). Mutant LRRK2 leads to the accumulation of misfolding intracellular protein accumulations, cell stress and apoptosis (Giasson et al. 2006, Zhu et al. 2006).

The importance of oxidative stress in PD pathology is further substantiated by the measurement of decreased levels of reduced glutathione in the brains of patients with PD (Holmay et al. 2013). Glutathione levels are low at very early stages of PD and correlate with disease severity (Riederer et al. 1989), and experimental induction of glutathione depletion leads to mitochondrial complex I dysfunction (Jha et al, 2000;). Reduced glutathione is an essential intermediary

metabolite that serves as the primary native cellular antioxidant. In a state of high oxidative stress, elevated levels of ROS outstrip the supply of glutathione (GSH) resulting in depletion of GSH and ROS-mediated cell death.

Given the important role of oxidative stress and mitochondrial pathology in PD, a redox-active therapy that could target key pathways in cellular OS response pathways may hold promise for the treatment of PD.

B. Rationale for the Study of EPI-589 in Parkinson's Disease

EPI-589 is a redox active molecule that has demonstrated potency (EC50 <100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with idiopathic and familial PD genetic subtypes including PINK1, parkin and LRRK2.

In these cell-based assays, primary fibroblasts from patients (and control) were pre-incubated with and without test compound, then treated with L-buthionine-(S,R)-sulfoximine (BSO), a GSH synthesis inhibitor, to initiate depletion of cellular GSH. GSH depletion has been shown to lead to OS and disruption of calcium homeostasis resulting in loss of the mitochondrial membrane potential and cell death. Under these conditions, the control cells are resistant to the stress and the fibroblast cells from patients with disease indications die within 36 to 48 hours. Pretreatment of cells with EPI-589 prior to initiation of GSH depletion potently protected against oxidative stress-mediated cell death, with EC_{50} response concentrations of 16 to 52 nM. (Table 1).

Table 1: Cell Line Rescue with EPI-589 in Parkinson's Disease Genetic Subtypes

	EPI-589 **EC_{50} (nM range)**
PINK1	26-36
LRRK2	16-18
parkin	42-52

C. Name and Description of Investigational Product

The IUPAC name of 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 derived from resolved (R)-Trolox®, a derivative of vitamin E in the form of a pale yellow to yellow solid. The EPI-589 drug product will be provided in a 250-mg tablet formulation.

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. In 28-day and 91-day repeat-dose toxicity studies in rat and cynomolgus monkey, the no observed adverse effect level (NOAEL) was 300 mg/kg/day, corresponding to combined mean Cmax values of 37,717 to 56,500 ng/mL (rat) and 14,300 to 16,417 ng/mL (monkey), and a combined mean area under the plasma concentration-time curve from time zero to the last measurable concentration (AUClast) value of 149,495 to 297,000 ng.h/mL (rat) and 47,300 to 67,656 ng.h/mL (monkey) (Studies 1660-038, 1660-039, 1660-063, and 1660-064).

A phase 1 clinical study demonstrated that healthy subjects administered 500 mg EPI-589 BID for 14 days showed a mean Cmax value of 1,890 ng/mL and a mean AUClast value of 5,240 ng.h/mL (Study EPI589-14-01). These plasma concentrations are well below the mean exposure values in monkey associated with the NOAEL in the toxicity studies, corresponding to safety margins of approximately 7- to 8-fold for the mean Cmax and 9- to 12-fold for the mean AUC.

During the 28-day repeat-dose toxicity studies, rat and monkey were exposed to up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-039 and 1660-038). The NOAEL for both studies was 300 mg/kg/day. Rats exposed to 1,000 mg/kg/day exhibited adverse 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 showing corresponding microscopic pathology. The majority of these findings were resolved following the 28-day recovery period. Monkeys exposed to 1,000 mg/kg/day showed significant test-article related morbundity that resulted in half the animals in the high dose group being euthanized on Days 3 and 4 and the remaining animals being euthanized on Day 9. These animals exhibited significant elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values, and microscopic findings in the kidney, liver, skeletal muscle, heart, and lymphoid tissues. In several of the animals the primary cause of morbidity was determined to be test-article related renal tubular degeneration/necrosis.

During the 91-day repeat-dose toxicity studies, rat and monkey were exposed to up to 300 mg/kg/day EPI-589 PO (Studies 1660-063 and 1660-064). The NOAEL for the rat study was 300 mg/kg/day and the no observed effect level (NOEL) for the monkey study was 300 mg/kg/day. [redacted] rats exposed to 300 mg/kg/day and [redacted] rats exposed to ≥ 100 mg/kg/day exhibited mild test-article related effects on hematology parameters consistent with hemolysis and bone marrow regeneration. These findings were not considered adverse.

Development and reproductive toxicology studies were conducted in rat and rabbit at doses up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-069, 1660-067, and 1660-068). The NOAEL for reproductive toxicity in rat was demonstrated to be 1,000 mg/kg/day (1660-069). The NOAEL

for developmental toxicity in rat and rabbit during the embryofetal studies was deemed to be 300 mg/kg/day (Studies 1660-067 and 1660-068). Rats exposed to 1,000 mg/kg/day exhibited 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. Rabbits exposed to 1,000 mg/kg/day exhibited 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 (Study EPI589-14-01) and rabbits exposed to 1,000 and 300 mg/kg/day EPI-589 is approximately 179- to 236-fold and 47- to 50-fold, respectively. 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 (Study AD58AS.502ICH.BTL); 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 (Study AD58AS.331ICH.BTL); and negative in the in vivo micronucleus assay in rat (Study AD58AS.125012ICH.BTL). These data indicate a low clinical mutagenicity risk.

Primary pharmacodynamics studies demonstrated that EPI-589 is a potent rescue agent in cellular models of diseases of energy metabolism and oxidative stress. In vitro cellular models utilizing primary human fibroblasts from patients with ALS, Parkinson's disease and other diseases characterized by high levels of oxidative stress, or striatal cells derived from mouse models of Huntingdon's disease were used to assess the potential of EPI-589 to mitigate the harmful effects of oxidative stress (Studies EPI-BA-000216, EPI-BA-000363, and EPI-BA-000362). Pretreatment of patient cells with EPI-589 potently protected against oxidative stress-mediated cell death in a concentration dependent manner. Furthermore, EPI-589 normalized 3-nitrosotyrosine (3NT) levels, a biomarker of oxidative stress, and increased glutathione levels in mouse striatal cells under oxidative stress conditions.

In secondary pharmacodynamics in vitro receptor/ion channel binding studies, EPI-589 did not significantly affect off-target molecular targets (Study EPI-BA-159). In safety pharmacology studies, EPI-589 did not significantly affect ion channel current in the hERG assay (Study 130719.FEK); did not affect ECG parameters during the 28-day and 3-month repeat-dose toxicology studies in monkey at doses up to 1,000 mg/kg/day (only Day 1 data collected for animals administered 1,000 mg/kg/day and up to Day 91 data collected for animals administered up to 300 mg/kg/day) (Studies 1660-038 and 1660-064); and did not change respiratory function or adversely impact neurobehavioral function in rat at doses up to 1,000 mg/kg (Studies 1660-051, 1660-050, and 1660-063).

In single dose exposure PK studies, EPI-589 was absorbed rapidly in rat, dog, and monkey, with mean T_{max} values ranging from .08 to 1 hour and mean T1/2 values ranging from 3.7 to 5.0 hours (Studies EPI-BA-53, EPI-BA-59, EPI-BA-72, and EPI-BA-302). EPI-589 does not significantly induce cytochrome P450 (CYP) enzymes and appears to be metabolized by reductases in the

liver cytosol and microsomal subcellular fractions and to a lesser extent by the family of CYP enzymes (Studies MC12M-0037 and MC14M-0018).

EPI-589 exhibited weak direct inhibition of CYP2B6, CYP2C8, CYP2C9, and CYP3A4/5 (both midazolam and testosterone as probe substrates) with estimated IC_{50} (μM) values and R values based on free plasma concentrations (shown in parentheses) of 28 (1.25), 40 (1.18), 92 (1.08), 34 (1.21), and 53 (1.13), respectively (Study MC14M-0020)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.

D2. Clinical Studies

Phase I Study EPI589-13-022 evaluated the pharmacokinetics, safety and tolerability of single ascending oral doses (SADs) of EPI-589 in healthy subjects and a preliminary evaluation of safety and tolerability data was performed. Sixteen AEs were reported in the 36 subjects who received administration of EPI-589. Ten subjects (27.8%) who received EPI-589 (and 2 subjects, 20% on placebo) reported AEs that were assessed as related. All were mild and resolved during the study, with the exception of a common cold (1 subject) and cold sore (1 subject). 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. Twenty-six subjects (65.0%) on EPI-589, and 8 subjects (80%) on placebo reported AEs. Twenty-four of 34 AEs were considered by the Investigator to be related to EPI-589. Nineteen subjects (47.5%) on EPI-589, and 6 subjects (60%) on placebo reported AEs that were assessed as related. All adverse events were mild, except for 1 AE which was moderate (unrelated brain contusion). All AEs were resolved during the study, with the exception of one, which was a common cold. 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 the MAD study it may be concluded that there is no objection to proceed with treatment with 250-mg, or 500-mg doses of EPI-589.

E. Human Pharmacokinetics

EPI-589 was fast absorbed following oral administration in SAD Study EPI589-13-022. The median C_{max} was attained approximately within 1 hour under fasted conditions after dosing. The median T_{max} values were attained in 0.50 to 1.00 hours over the dose range of 50 to 1000 mg under fasted conditions and 3.01 hours at the 500 mg dose level under fed conditions. Mean half-life ranged from 5.55 to 10.7 hours over the dose range of 50 to 1000 mg under fasted conditions and 4.91 hours at the 500 mg dose level under fed conditions. Half-life was independent of the dose levels over the dose range of 50 to 1000 mg under fasted conditions. The rate of EPI-589 absorption, as measured by C_{max}, was decreased by 24.07% under fed conditions at the 500 mg

dose level. The extent of absorption as measured by AUCs (AUC_{0-t} or AUC_{0-inf}) was not affected under fed conditions in the 500 mg dose groups.

In MAD study EPI589-14-01, 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 of various ages and smoking status. No significant effects of age or smoking on EPI-589 pharmacokinetics were observed in this study. Dose proportionality existed in the exposures (AUC_{0-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

EPI589-15-002: A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects.

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 meals.

H. Compliance Statement

This study will be conducted in full accordance with all applicable research policies and procedures, the EU Clinical Trials Directive, all applicable EU and 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, will obtain consent and will 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.

I. Relevant Literature and Data

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

IV. STUDY OBJECTIVES

A. Primary Objective

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 PD.

B. Secondary Objectives

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

1. Glutathione cycle biomarkers as measured in blood, cerebral spinal fluid, and urine
2. Clinical disease state as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D
4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA)
5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery & Asberg Depression rating scale (MADRS)
6. Pharmacokinetics
7. Hematology, blood chemistry, electrocardiogram

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V. INVESTIGATIONAL PLAN

A. General Schema of Study Design

Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues.

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects. Given that the investigational drug targets an enzyme key to glutathione synthesis and that glutathione depletion has been found to be associated with PD, we are seeking to determine the safety and potential biochemical benefit of EPI-589 in PD subjects as assessed by glutathione cycle biomarkers. If we determine that there are a subset of idiopathic PD patients—whether due to disease stage or baseline biomarker profile—who are more likely to be EPI-589 responsive, we will seek to enroll additional numbers of these subjects in the adaptive phase so that we can increase the number of likely biomarker responsive subjects. EPI-589 will be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues.

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 run-in scans, CNS, blood-based biomarker, urine-based biomarker and clinical measurements will be collected.

A3. Baseline

Baseline assessments, scans, blood-based biomarker, urine biomarker, 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-based biomarker, urine biomarker, and clinical measurements will be collected at Day 29 (± 3 days) and Day 85 (± 3 days).

A5. End of Treatment

End of treatment data will be collected at the last study visit Day 85 (± 3 days).

AEs reported as ongoing at Day 85 (± 3 days) and/or any concomitant medications associated with such events 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.

A6. Post-Treatment Follow-up

Post-Treatment Follow-up will be at least 10 days and up to 30 days after last dose: AE/SAE and concomitant medication assessments conducted by telephone. Additional assessments to be determined at Investigator discretion.

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 biomarker and clinical baseline measurements. EPI-589 will then be administered for 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues. A post-treatment follow-up will be conducted at least 10 days and up to 30 days after last dose.

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

This study will be conducted at five study sites:

- [redacted] Germany
- [redacted], UK
- [redacted] USA
- [redacted] USA
- [redacted] USA

Approximately 40 subjects with PD are projected:

- 20 with genetically-defined subtypes
- 20 PD idiopathic PD

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the same study protocol and outcome metrics.

D. Study Population

D1. Inclusion Criteria (all subjects)

1. Hoehn and Yahr stage ≤ 3.0
2. Ambulatory with or without assistance
3. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., hormonal methods, including oral, subcutaneous, and intrauterine; barrier methods, including [redacted] condom, [redacted] condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study treatment.
4. Willingness and ability to comply with study procedures
5. If on medications and supplements for PD, then regimen must be stable for 60 days prior to enrollment
6. Abstention from use of other investigative or non-approved drugs for the duration of the trial

For Idiopathic Subjects

7. A diagnosis of idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit
8. Age 40 to 75 years
9. Within 5 years of diagnosis of Parkinson's disease

For Genetic Subtype Subjects

10. A confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LRKK2 or other mitochondrial genetic subtype
11. Age 21 to 75 years

D2. Exclusion Criteria

1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation
2. Vitamins E and C beyond the recommended daily allowance
3. Other Parkinsonian disorders
4. MoCA score of <24
5. Revised Hamilton Rating Scale for Depression ≥ 11
6. Parkinsonism due to drugs or toxins
7. Diagnosis of any other clinically significant neurologic disease that will confound the assessment of effect of study drug on disease progression
8. Malignancy within past two years
9. Pregnant or plans to become pregnant or breast feeding
10. History of stroke
11. History of brain surgery
12. Hepatic insufficiency with liver function tests (LFTs) > 3 times upper limit of normal
13. Renal insufficiency as defined by creatinine > 1.5 times normal

14. End stage cardiac failure
15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD

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VI. STUDY PROCEDURES

A. Screening Visit

Screening evaluations will be performed within two months of first dose. The Investigator will inform each prospective subject of the nature of the study, explain the potential risks, and must 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. Receipt and review of previous testing including genetic tests
4. Physical examination including vital signs
5. Height and weight
6. 12-lead ECG
7. Laboratory assessments for hematology, coagulation, and serum chemistry (See Sections VII.D3.a and VII.D3.b)
8. Urine pregnancy test (women of childbearing potential must have a negative urine pregnancy test; see Section VII.D3.c)
9. MDS-UPDRS
10. MoCA
11. DaTscan (for idiopathic subjects only)
12. Revised Hamilton Rating Scale for Depression
13. AE/SAE assessments
14. Concomitant medications assessment (last 60 days prior to enrollment)

A1. Run-in Assessments

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 within one month for Run-in assessments. These will 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. Blood-based glutathione cycle biomarkers
2. CNS biomarkers (lumbar puncture)
3. Urine biomarkers
4. Timed motor tests (for subjects on dopamine therapy)
5. AE/SAE assessments
6. Concomitant medications review

B. Treatment Phase

After the Run-in phase, the subject must return to the clinic within 30 days (± 3 days) for baseline assessments. In-clinic study visits are scheduled at Month 1 and Month 3. The Month 2 study assessments can be conducted via telephone. End of treatment assessments will be

conducted 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 including vital signs
2. Height and weight*
3. 12-Lead ECG*
4. Blood-based GSH cycle biomarkers
5. Urine-based biomarkers
6. Laboratory assessments for hematology, coagulation and serum chemistry*
7. Urine pregnancy test ([redacted] of child bearing potential)
8. C-SSRS (Columbia Suicide Severity Rating Scale)
9. MDS-UPDRS
10. NMSS, PDQ-39, EQ-5D
11. BDI, MADRS
12. Timed motor tests (for subjects on dopamine therapy)
13. AE/SAE assessments
14. Concomitant medications review

* Screening results for these assessments may be used if obtained within 1 month of Baseline and if they are completed under fasted conditions.

B2. Study Visit Assessments

- Month 1 Clinic Visit (Day 29 ± 3 days):

The following will be assessed or performed at the Month 1 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry
5. Urine pregnancy test (females of child bearing potential)
6. C-SSRS
7. Blood-based GSH cycle biomarkers
8. Urine-based biomarkers
9. MDS-UPDRS
10. Pharmacokinetics: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.
11. AE/SAE assessments
12. Concomitant medications review

- Month 2 Visit (Day 57 ± 3 days)

Month 2 assessments can be conducted by telephone and must include review of:

1. AE/SAE assessments
2. Concomitant medication

- Month 3 Clinic Visit (Day 85 ± 3 days)

The following will be assessed or performed at the Month 3 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry
5. Urine pregnancy test (females of child bearing potential)
6. C-SSRS
7. Blood-based GSH cycle biomarkers
8. Urine-based biomarkers
9. CNS biomarkers
10. MDS-UPDRS
11. Pharmacokinetics: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.
12. AE/SAE assessments
13. Concomitant medications review
14. MoCA
15. NMSS, PDQ-39, EQ-5D
16. BDI, MADRS
17. Timed motor tests (for subjects on dopamine therapy)

B3. Pharmacokinetics

Plasma concentration samples will be collected from the first 10 subjects to complete 1 month of therapy at each site, at the following time points:

- Month 1 (Day 29 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose
- Month 3 (Day 85 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose

B4. Early Termination Study Visit

Subjects who terminate from the study after receiving first dose and prior to the completion of all scheduled visits should have the end of treatment visit assessments completed as soon as possible.

C. End of Treatment Visit

End of treatment visit takes place at Month 3 (Day 85 ± 3 days) and includes the assessments listed in Section VIB2 Study Visit Assessments.

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. Post-Treatment Follow-up

Post-Treatment Follow-up will be at least 10 days and up to 30 days after last dose, with AE/SAE and concomitant medication assessments conducted by telephone. Additional assessments to be determined at Investigator discretion.

E. Unscheduled Visits

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

F. Concomitant Medication

Any medication taken by a subject ≤ 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 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 consulting the Investigator.

G. Prohibited Medications

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

1. Vitamins E and C beyond the recommended daily allowance
2. Participation 3 months prior to and for the duration of the study in a trial of a device, drug or other therapy for PD

H. Subject Withdrawals

Subjects receive study treatment until treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The following conditions require subject discontinuation from all study treatment:

1. At their own request or at the request of their legally authorized representative

2. If a subject experiences an adverse event that is deemed related to treatment with EPI-589 and in the Investigator's or the Sponsor's medical judgment continuation of treatment would be detrimental to the subject.
3. At the specific request of a regulatory agency for termination of treatment of an individual subject or all subjects under the protocol
4. Subject participation in another clinical study using an investigational agent or investigational medical device
5. Use of prohibited medications such as vitamins E and C beyond the recommended daily allowance.
6. Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use medically accepted methods of contraception
7. If a subject becomes pregnant.
8. Significant noncompliance with the protocol in the opinion of the Investigator or the Sponsor

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 should 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 PD.

B. Secondary Endpoints (Efficacy)

1. Blood-based biomarkers
2. CNS-based biomarkers
3. Urine-based biomarkers
4. MDS-UPDRS
5. NMSS
6. PDQ-39
7. EQ-5D
8. MoCA
9. BDI
10. MADRS
11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)
12. Pharmacokinetics

C. Secondary Endpoints (Safety)

1. Routine assessments of AEs and SAEs
2. Dose limiting toxicities
3. Routine serum chemistries with liver function tests
4. C-SSRS
5. Routine hematology tests with coagulation tests
6. Electrocardiogram

D. Screening and Baseline Evaluation

D1. Physical Examination

Complete physical exams will be conducted (excluding genital/rectal exam) at protocol specified study visits. 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, heart, abdomen, and extremities.

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).

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

D2. Height and Weight

Weight (kg) will be measured in ordinary indoor clothing (i.e., street clothes, scrubs, etc.) with shoes off. Height will be recorded in centimeters (cm).

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.

D3. Laboratory Evaluations

Subjects 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 I).

a. Hematology

a. Erythrocytes: red blood cell (RBC) count, hematocrit, hemoglobin, mean corpuscular volume (MCV)
b. Leukocytes: white blood cell count (WBC) and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)
c. Platelets: platelet count
d. Coagulation: prothrombin time (PT) with INR, and partial thromboplastin time (PTT)

b. Serum chemistry

a. Liver: Alkaline Phosphatase (ALP), ALT (serum glutamic-pyruvic transaminase [SGPT]), AST (serum glutamic-oxaloacetic transaminase [SGOT]), bilirubin (total and direct), gamma-glutamyl transferase (GGT), and lactic dehydrogenase (LDH)
b. Renal: blood urea nitrogen (BUN), and creatinine
c. Electrolytes: sodium, potassium, chloride and carbon dioxide (CO_2)
d. General: creatine phosphokinase (CPK), total protein, albumin, calcium, magnesium, glucose, phosphate
e. Lipids: cholesterol (total), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL), cholesterol, and triglycerides

c. Urine pregnancy test

1. Human chorionic gonadotropin (HCG) beta subunit will be measured on all female subjects of childbearing potential.

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.

Diagnoses associated with any NIH Common Terminology Criteria for Adverse Events (CTC v4.03) Grade 3 or 4 laboratory abnormalities will be recorded as adverse events (AEs**)** on the CRF. Repeated and verified ≥ Grade 3 laboratory tests will be reported as an AE to the IRB per institutional requirements. The recorded event 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.

D4. 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.

E. Sample Collection Procedures, Bioanalytical Methods and Sample Shipment

Subject samples will be identified by unique sample codes.

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

F. Efficacy Evaluations

F1. Glutathione Cycle Biomarkers

Blood, urine, and CNS levels of oxidized and reduced GSH as well as GSH metabolites will be used to evaluate EPI-589 target engagement and ability to correct a key biochemical aspect of disease pathology.

F2. Parkinson's Disease Rating (MDS-UPDRS)

The MDS-UPDRS is a tool for monitoring the impact of PD, the degree of disability caused, and complications from treatment. Part I evaluates nonmotor experiences of daily living; Part II evaluates motor experiences of daily living; Part III is a motor examination and includes the Hoehn and Yahr scale; Part IV examines motor complications (e.g., motor fluctuations and dyskinesias).

Several questions from Part I and all questions from Part II are designed to be amenable to a patient/caregiver questionnaire format; the remaining interview (Part I and Part III) and examination (Part IV) are designed with the expectation they can be completed within 30 minutes. Each item is measured on a five-point scale.

F3. Non-motor Symptoms (NMSS)

Non-motor symptoms are evaluated using the NMSS which is divided into 30 questions in 9 different domains including such symptoms as dribbling saliva, constipation, depression, sleep disorders, apathy, hallucinations and dementia. Symptoms are quantified based on their severity (using a scale of 0 to 3) and frequency (using a scale of 0 to 4). The final cumulative scores are derived from adding up the product of the frequency score times severity score for each of the 30 questions.

F4. Parkinson's Disease Questionnaire (PDQ-39)

PDQ-39 is a self-administered questionnaire for patients with PD that has 39 questions relating to eight key areas of health and daily activities, including both motor and non-motor symptoms. It is scored on a scale of 0 to 100, with lower scores indicating better health, and high scores more severe symptoms.

F5. EQ-5D

EQ-5D is a questionnaire designed to provide measures of health-related quality of life states, consisting in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

F6. Montreal Cognitive Assessment (MoCA)

MoCA is a 30-point questionnaire for cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Severity ranges are approximately: 26 to 30 normal; 18 to 26 mild cognitive impairment; 10-17 moderate cognitive impairment; < 10 severe cognitive impairment.

F7. Beck Depression Inventory (BDI)

The BDI is a self-reporting inventory that measures characteristic attitudes and symptoms of depression, including physical symptoms. Twenty-one questions have four responses each (rated 0 to 3) with a total cumulative score scale ranging from 1-10 considered normal) > 40 (extreme depression).

F8. Montgomery and Asberg Depression rating scale (MADRS)

The MADRS is a clinician-rated tool for measuring changes in depressive symptom severity. Ten core symptoms and cognitive features are rated on a severity scale of 0 to 6. Higher scores indicate increasing depressive symptoms.

F9. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)

Timed motor tests are simple, objective, quantitative measures for the assessment of Parkinson's disease. They include, in an on-medication and an off-medication state, timed recorded physical movements.

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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.

A1. Analysis Populations

Demographic characteristics and baseline efficacy data will be presented and summarized by treatment group for all subjects in the efficacy intent to treat (EITT) population. Demographic information will also be summarized by treatment group 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. CNS biomarkers
3. Urine-based biomarkers
4. MDS-UPDRS
5. NMSS
6. PDQ-39
7. EQ-5D
8. MoCA
9. BDI
10. MADRS
11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)
12. Pharmacokinetics

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 PD.

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 40 subjects (20 with genetically-defined subtypes of PD and 20 idiopathic PD subjects). Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker-responsive idiopathic PD subjects to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the same study protocol and outcome metrics.

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IX. STUDY MEDICATION

A. Description

EPI-589 is presented as an immediate release film-coated tablet. Each tablet contains 250 mg of EPI-589 and the following compendial excipients: lactose, 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, in compliance with 21 CFR 312.6 and Eudralex Vol. 4 EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13

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 HPDE 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]).

C. 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 verification with subject-completed diary cards and returned used drug supply.

D. Drug Accountability

Dosing information will be captured on a subject Dosing Diary Form. This form is part of the 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 Investigator study file to assure the study medication is 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 either be 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 in accordance with the IRB policies and as detailed below. AEs that are not serious will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

B1. Safety Guidance

Based on the known clinical manifestations of Parkinson's disease, we expect that many AEs could occur during the course of the trial that are well documented to occur as the results of the natural history of this disease. These include, but are not limited to worsening neuromuscular function, depression, decline in cognitive function, loss of vision and other ophthalmological symptoms, loss of coordination and loss of speech.

As there are no data available regarding EPI-589 phototoxicity, investigators are to advise subjects to take measures to minimize exposure to ultraviolet (UV) light for the duration of the study and for one week after the last dose.

Edison Pharmaceuticals 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, Edison Pharmaceuticals should be provided with a copy of any post-mortem findings, including histopathology.

C. Definition of an Adverse Event

C1. Adverse Event

An 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" or "AE".

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)

An 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; or
5. A congenital anomaly/birth defect.

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 subject 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 an SAE which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether other AEs, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject, require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

[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; follow-up of the pregnancy, fetus, and child will continue for at least 8 weeks after delivery. While pregnancy itself is not considered an

AE or SAE, all pregnancies should be reported using the same process as for SAEs. Any pregnancy complications or an outcome other than a healthy, normal outcome will be recorded as an AE or SAE.

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.

C3. Non-serious Adverse Event

A non-serious AE 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 and reappears with re-introduction 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 indicated.

Grade 2 – Moderate limitation in activity, some assistance may be needed; minimal noninvasive medical intervention/therapy indicated.

Grade 3 – Severe limitation in activity, assistance usually required; medical intervention/therapy required; hospitalization or prolongation of hospitalization indicated; disabling.

Grade 4 – Extreme limitation in activity, significant assistance required; urgent medical intervention/therapy required; life-threatening consequences.

Grade 5 – Death

C6. Definition of Unexpected Adverse Event

Any AE, the specificity or severity of which is not consistent with those listed in the current investigator's brochure is considered "unexpected."

C7. Notification of SAEs

The Investigator is responsible for promptly notifying the IRB/IEC of all study on-site SAEs 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 MedWatch or CIOMs form (as appropriate).

SAEs (whether unexpected or expected AEs) must be documented on the designated SAE form. The SAE must be reported to the medical expert and appropriate Edison or Edison-assigned pharmacovigilance staff within 24 hours, according to regulatory, Sponsor, or ICH-E6 Good Clinical Practice, followed by the SAE form within two 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 Investigator and/or Medical Expert must also inform the Study Monitor and the Sponsor in all cases. Any SAEs must also be reported to the IRB/IEC. The Sponsor or designee will ensure that all legal reporting requirements are met.

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 a follow-up SAE forms.

The instructions to sites for the completion of SAE reports give detailed guidance on the reporting of SAEs and AEs initially reported as non-serious that become serious. When a non-

serious event becomes serious, details must be forwarded immediately to the Medical expert and Edison or Edison-assigned 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 reported to the relevant competent authorities.

In the US, all fatal or life-threatening suspected unexpected serious adverse events assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA as soon as possible (i.e., by telephone or facsimile transmission), but no later than 7 calendar days after first knowledge by the Sponsor that a report qualifies as a suspected unexpected fatal or life-threatening reaction. All unexpected serious adverse events, other than fatal or life-threatening, assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA within 15 calendar days from the day the Sponsor determines that the information qualifies as a SUSAR.

In the UK, the Sponsor or trial investigator must act immediately or at least within 24 hours after becoming aware of a SUSAR by informing the MHRA's Clinical Trial Unit by telephone. The MHRA must then be informed in writing within 3 days of the incident. All SUSARs originating in the UK or originating outside the UK involving the same medicinal product are to be reported. Fatal or life-threatening SUSARs are to be reported as soon as possible, but no later than after 7 days. Any additional relevant information must be sent within 8 days of the report. Non-fatal or non-life-threatening SUSARs are to be reported as soon as possible but no later than 15 days after becoming aware of the reaction.

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. All SAEs should be followed until either resolved or stable.

C9. Dose Modification Guidelines

In the event that any patient develops elevated INR ≥ grade 2 in severity (> 1.5-2.5 x ULN) per CTCAE criteria version 4.0 thought to be related to treatment with EPI-743, administration of EPI-589 will be reduced by 1/2 to 50 percent of the starting dose. Should the INR toxicity not resolve to at least grade 1 in severity within two weeks of the initial dose reduction, administration of EPI-589 may either be further reduced or discontinued.

Once a patient's dose is reduced due to elevated INR thought to be related to study drug administration, their dose should not be re-escalated.

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 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.

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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 Edison 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 Edison. 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 Edison 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 (0.001%), a systematic review of the database will be undertaken and corrections will be made to achieve an error rate of less than 0.001%.

AEs will be coded using MedDRA, version (14.3). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary, March 2014.

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 or 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, and the General Data Protection Regulation (GDPR).

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 EPI-589-14-01 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 PD. Therefore, we cannot assure that subjects will benefit from treatment with EPI-589. Potential benefits may manifest in a variety of ways, such as in disease-related parameters, functioning, and quality of life.

G3. Risk-Benefit Assessment

There are no effective and/or approved disease modifying treatments available for PD, 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 hold benefit for patients with PD. This is the first study to better understand EPI-589 target engagement and potential therapeutic

benefit in subjects with PD. 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 Edison (such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by Edison and are unpublished), are confidential and must remain the sole property of Edison. 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 Edison 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 Edison. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

This Study is part of a multicenter clinical research study. Accordingly, 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 while this Study is being conducted at other center/s. Only after the completion of this Study at all other centers, provision of the data to the FDA or EMA for review and comment, and publishing the combined data from all of the centers, may the Principal Investigator 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 Edison, Edison will allow the Investigator or CRO 60 days for full review of the manuscript before publication.

XIII. LIST OF ABBREVIATIONS

AE	adverse event
AI	accumulation index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AR	accumulation ratio
BDI	Beck Depression Inventory
BID	twice daily
BSO	L-buthionine-(S,R)-sulfoximine
C-SSRS	Columbia-Suicide Severity Rating Scale
CBC	complete blood count
CFR	Code of Federal Regulations
CK	creatinine kinase
CNS	central nervous system
CoQ10	Coenzyme Q 10
CRF	Case Report Form
CRO	Contract Research Organization
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DaT	dopamine transporters
DSMB	data safety monitoring board
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EITT	efficacy intent-to-treat
EPDA	European Parkinson's Disease Association
EU	European Union
%F	percent fluctuation
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GCRC	good clinical research practice
GDPR	General Data Protection Regulation
GSH	glutathione
GSSG	glutathione disulfide
HDPE	high density polyethylene
hERG	human Ether-a-go-go Related Gene
HCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HMPAO	hexamethylpropylene amine oxime
ICF	informed consent form
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUPAC	International Union of Pure and Applied Chemistry

kg	kilogram
Λz	apparent terminal constant
LFT	liver function test
MAD	multiple ascending (oral) dose
MADRS	Montgomery and Asberg Depression rating scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
mg	milligram
mL	milliliter
MoCA	Montreal Cognitive Assessment
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPV	mean platelet volume
mtDNA	mitochondrial DNA
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NF	National Formulary
nM	nanomolar
NMSS	Non-motor Symptoms Scale
NOAEL	no observed adverse effect level
NQ01	NAD(P)H Quinone oxidoreductase 1
OD	once daily
OTC	over-the-counter
PD	Parkinson’s disease
PDQ-39	39-Item Parkinson’s Disease Questionnaire
PO	by mouth
PT	Prothrombin Time
PTT	Partial Prothrombin 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
SAD	single ascending (oral) dose
SAE	serious adverse event
SD	standard deviation
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
UV	ultraviolet

XIV. SIGNATURE OF SPONSOR

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 CFRparts 50, 54, 56, and 312.

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

Date: [3 Oc(2o:' ignature: [redacted]

[redacted]
Edison Pharmaceuticals, Inc.
350 North Bernardo Ave
Mountain View, CA 94043

XV. REFERENCES

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Summary of Changes

Amendment 3.0

EPI589-15-002

A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects

Protocol Number	EPI589-15-002
Original Protocol Date	27 April 2015
Amendment 1.0 Date	09 September 2015
Amendment 2.0 Date	04 January 2016
Amendment 3.0 Date	10 October 2016
Study Sponsor	Edison Pharmaceuticals, Inc. 350 North Bernardo Avenue Mountain View, CA 94043
Sponsor's Representative	[redacted] Edison Pharmaceuticals, Inc. 350 North Bernardo Avenue Mountain View, CA 94043

KEY CHANGES TO THE PROTOCOL

Amendment 3.0 provides the following changes and their rationales:

Change	Rationale
• Added the new list of investigators and investigative sites	• To complete the list of investigators and sites
• Revision of inclusion and exclusion criteria regarding disease severity and prohibited meds	• To allow for the study of drug safety, tolerability and biomarkers in a larger cohort of idiopathic Parkinson's disease subjects
• Added the term "for idiopathic subjects" to DaTscan , "fasting" for blood-based glutathione cycle biomarkers in schedule of assessments	• For better clarity
• Changed the MDS-UPDRS assessment from run-in to screening visit	• Hoehn and Yahr is a screening assessment and is part of MDS-UPDRS assessment
• Changes in laboratory evaluations, NIH common terminology criteria, etc	• To clarify aspects of the protocol which have been previously documented in administrative letters
• Dose modifications guidelines	• To clearly define guidelines for dose modifications

DESCRIPTION OF CHANGES TO THE PROTOCOL

Changes to the protocol by section appear in the table below. Administrative and editorial clarifications, corrections or adjustments may not be individually identified.

In this summary document, ***bold italic*** font indicates additions to existing text, and ~~strikethrough~~ font indicates deleted text. The actual amended protocol does not include bold or strikethrough font to indicate changes.

Protocol Section	Modification
Synopsis	Investigators and Investigative Sites: • [redacted] ***Germany*** • [redacted] UK • [redacted] USA • [redacted] ***USA*** • [redacted] ***USA***
Synopsis	Planned number of subjects Approximately 40 subjects (20 with genetically-defined subtypes of PD and 20 ~~drug naïve~~ ***idiopathic PD*** subjects). (Adaptive design component allows enrollment of up to 20 additional subjects with idiopathic PD to try to achieve a total of 20 subjects that have a biomarker response to EPI-589.)
Synopsis	Inclusion Criteria ***(for all subjects)*** 1.Hoehn and Yahr stage ≤ ~~2.5~~ ***3.0*** 5. If on medications and supplements for PD ~~drugs~~, then ~~medication~~ regimen must be stable for 60 days prior to enrollment ~~Stable medication regimen of PD drugs for 30 days (except 60 days for rasagiline) prior to enrollment~~. For Idiopathic Subjects: ~~7. For idiopathic subjects:~~ a diagnosis of ~~early~~ idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit ~~8. *For idiopathic subjects* must not yet require symptomatic medications for PD and not expected to require such treatment before the end of the study~~ ~~9. *For idiopathic subjects*:~~ age 40 to 75 years ~~10. *For idiopathic subjects*:~~ within 5 years of diagnosis of Parkinson's disease For Genetic Subtype Subjects: ~~11. For genetic subtype subjects:~~ a confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, ~~LARK2~~ ***LRRK2*** or other mitochondrial genetic subtype ~~12. For genetic subtype subjects: stable medication regimen of PD drugs for 30 days (except 60 days for rasagiline) prior to enrollment~~

Synopsis

Exclusion Criteria

2. Use of afltio Eiea:Bts. Sfl@eifieally v Vitamins E and C beyond the recommended daily allowance

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II. Schedule of Assessments and Dosing Schedule

Tests	-2 to -1 Months		DayO		Month 1	Month 2	Month3 End of Treatment Visit	Post-Treatment Follow-up
	Screening	Run-in *(upto 30 days from screening)*	Baseline *(27-33 days from run-in)*		Day29 (±3 days)	Day 57d (±3 days)	Day85 (±3 days)	Up to30 Days after Last Dose•
Infonued consent				***Dayl First Dose***				
Inclusion/Exclusion criteria								
Past Medical histo1y								
Previous genetic testing review								
Physical exam & Vital signs								
Height & weight			•					
12-leadECG			•					
Hematology (including coagulation panel)			•		☛		☛	
Semm Chemistiy			•		☛		☛	
Pregnancy testb								
C-SSRS								
Montreal Cognitive Assessment								
DaTscan *(for idiopathic subjects)*								
Revised Hamilton Rating Scale for Depression								
Subject enrolls in study		X						
Fasting blood-based glutathione cycle biomarkers								
Lumbar puncnu·e (CNS biomarkers)								
Urine-based biomarkers								

	MDS-UPDRS		**+-**						
	Timed motor tests (for subjects on dopamine therapy)								
	NMSS, PDQ-39, EQ-5D								
	BDI,MADRS								
	Dmgplasma concentration<					<		<	
	AE/SAE assessment	-	-	-		-	d,-	d,-	-
	Concomitant medications assessment						d	d	•
	Post-Treatment Assessments•								•

a. Screening values can be used if done within one month of baseline *and if* ***completed under fasted conditions***
- Female subjects of childbearing potential must have a negative pregnancy test.
c. Full plasma concentration profile w-ill be obtained at Time= 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours aft.er dosing from the fast 10 subjects to complete 1 month of therapy at each site.12 *hour* ***PK*** *can be obtained at time 0.*
d. Month 2 assessments can be donebytelephone. Any new AEs and associated concomitant medications repo1ted at Month 3 must be followed for 30 days; this follow up may be conducted by telephone.
e. AE/SAE and concomitant medication assessments conducted by telephone at least 10 days after last dose. Additional assessments determined at Investigator discretion. SAEs are tra cked from the time ICF is signed and all other AEs are tracked from the time first dose is administered;
r. The baseline and all subsequent laboratory assessments should be obtained under fasting conditions.

IV. **Investigational Plan**

A. General Schema of Study Design

If we eefel'mtfto tfia f tfiet·e et·e a, s:4sef sf s:4jeefs • rtfft ftSRBal le!,!els sf gk-1f&fatsfte • ,i;as 00 a0t eem0asa·ate ei:0ehemi:eal ehaages feU0wi:Bg 9fYg aemi:Bi:sa·ati:0a, aae a s:4set 0{ stte:ieets '•¥tfh law le•,•els eheatteee gbtethtefte • rhe ea res13efte ta 9fYg a·eMmeftf, we • rsHle seelE fs em·sUeeetftsft&l tets13Mhte 12:Qstte:ieefs • rtfft ls•NglHfMfttsfte le!,!els fs a,ehte•,•e 8: fttgftet'1t:-11:ft8er ef SHe:jeefs tft • rft91:ft • re ee:-1le Hfteersfafte tfie eteeaemtea:l effeets ef tfie i:B:resttgMt¥e 9fYg 8:fte tfs 13eteftfta:1 ehBtea:ltfftj38ef a-s assesses ej' the smey 9'..-¼f89H¼9 mea·i:es. e:PI ◆g9 • .ii:Uee aemi:Btsfe1·ee :Ee!' :-113 f9 J IB9Bfhs Eg◆ BajlS .I. J BajlSj :-mless etseeftfttt:-¼ee :EE)f sa::fefy er telera:etldy tSSHes.

I/we determine that there are a subset of idiopathic ***PD*** *patients-whether due to disease stage or baseline biomarker profile-who are more likely to be EPI-589 responsive, we will seek to enroll additional numbers of these subjects in the adaptive phase so that we can increase the number of likely biomarker responsive subjects. EPI-589 will be administered/or up to 3 months (85 days± 3 days) unless discontinued for safety or tolerability issues.*

C. Study Duration, Enrollment and Number of Sites

Duration of Subject Treatment
Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues. A post-treatment follow-up will be conducted ***at least 10 days*** and up to 30 days after last dose.

Total Number of Study Sites/Total Number of Subjects Projected

This study will be conducted at ~~two~~ ***five*** study sites:

- [redacted] ***Germany***
- [redacted] UK
- [redacted] USA
- [redacted] ***USA***
- [redacted] ***USA***

Approximately 40 subjects with PD are projected:

20 with genetically-defined subtypes

20 ~~PD drug naïve~~ ***idiopathic PD***

D. Study Population

D1. Inclusion Criteria
Inclusion Criteria ***(for all subjects)***

1.Hoehn and Yahr stage ≤ ~~2.5~~ ***3.0***

5. If on medications and supplements for PD ~~drugs~~, then ~~medication~~ regimen must be stable for 60 days prior to enrollment

~~Stable medication regimen of PD drugs for 30 days (except 60 days for rasagiline) prior to enrollment~~.

For Idiopathic Subjects:

~~7. For idiopathic subjects:~~ A diagnosis of ~~early~~ idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit
~~8. *For idiopathic subjects* must not yet require symptomatic medications for PD and not expected to require such treatment before the end of the study~~
~~9. *For idiopathic subjects*:~~ Age 40 to 75 years
~~10. *For idiopathic subjects*:~~ within 5 years of diagnosis of Parkinson's disease

	For Genetic Subtype Subjects ~~11. For genetic subtype subjects:~~ a confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, ~~LARK2~~ ***LRRK2*** or other mitochondrial genetic subtype ~~12. For genetic subtype subjects: stable medication regimen of PD drugs for 30 days (except 60 days for rasagiline) prior to enrollment~~ D2. Exclusion Criteria 2. ~~Use of antioxidants, specifically v~~ Vitamins E and C beyond the recommended daily allowance ~~For Idiopathic Subjects~~ ~~16. For idiopathic subjects: use of any MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease for idiopathic subjects~~ ~~17. For idiopathic subjects: use of nortriptyline or fluvoxamine 60 days prior to enrollment~~
VI.	Study Procedures A. Screening Visit ***9. MDS—UPDRS*** ***13. AE/ SAE Assessments*** *A1.* Run-in Assessments ~~4. MDS UPDRS~~ ***5. AE/ SAE Assessments*** B1. Baseline Assessments ***13. AE/ SAE Assessments*** * Screening results for these assessments may be used if obtained within 1 month of Baseline ***and if they are completed under fasted conditions.*** G. Prohibited Medications The following are prohibited while the subject is on study treatment:

	1. ~~Use of antioxidants, specifically v~~ Vitamins E and C beyond the recommended daily allowance 2. Participation 3 months prior to and for the duration of the study in a trial of a device, drug or other therapy for PD 3. ~~Use of MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease for idiopathic subjects~~ 4. ~~Use of nortriptyline or fluvoxamine~~ H. Subject Withdrawals 2. If a subject experiences a***n*** ~~serious or severe~~ ***adverse*** event that is deemed related to treatment with EPI-589 and in the Investigator's or the Sponsor's medical judgment continuation of treatment would be detrimental to the subject. 5. Use of prohibited medications such as vitamins E and C beyond the recommended daily allowance. ~~nortriptyline or fluvoxamine; and, for idiopathic subjects, MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease~~
VII.	Study End Points and Evaluations D3. Laboratory Evaluations ~~The following variables will be collected at various times (as detailed in Section I).~~ ~~1. 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 (WBC) 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) with INR, partial thromboplastin time (PTT), activated (aPTT)~~ ~~2. Serum chemistry~~ ~~1. Liver: Alkaline Phosphatase (ALP), ALT (serum glutamic pyruvic transaminase [SGPT]), AST (serum glutamic oxaloacetic transaminase [SGOT]), bilirubin~~

~~(total and direct), gamma glutamyl transferase (GGT), and lactate dehydrogenase (LDH)~~

~~2. Renal: blood urea nitrogen (BUN), and creatinine~~

~~3. Electrolytes: sodium, potassium, chloride, and carbon dioxide (CO2) as bicarbonate~~

~~4. General: creatine phosphokinase (CPK), creatine kinase (CK), and troponin (at baseline only); total protein, 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~~

D3. Laboratory Evaluations

The following variables will be collected at various times (as detailed in Section I).

1. Hematology

a. Erythrocytes: red blood cell (RBC) count, hematocrit, hemoglobin, , mean corpuscular volume (MCV)

b. Leukocytes: white blood cell count (WBC) and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)

c. Platelets: platelet count

d. Coagulation: prothrombin time (PT) with INR, and partial thromboplastin time (PTT)

2. Serum chemistry

a. Liver: Alkaline Phosphatase (ALP), ALT (serum glutamic-pyruvic transaminase [SGPT]), AST (serum glutamic-oxaloacetic transaminase [SGOT]), bilirubin (total and direct), gamma-glutamyl transferase (GGT), and lactic dehydrogenase (LDH)

b. Renal: blood urea nitrogen (BUN), and creatinine

c. Electrolytes: sodium, potassium, chloride and carbon dioxide (CO_2)

d. General: creatine phosphokinase (CPK), total protein, albumin, calcium, magnesium, glucose, phosphate

e. *Lipids: cholesterol (total), high-density lipoprotein (HDL) cholesterol*, low-density lipoprotein (LDL), cholesterol, and triglycerides

Diagnoses associated with any NIH Common Terminology Criteria for Adverse Events (CTC v4.03) Grade 3 or 4 laboratory abnormalities will be recorded as adverse events (AEs) on the CRF. Repeated and verified ≥ Grade 3 laboratory tests will be reported as an ***AE*** ~~SAE~~ to the ~~Sponsor and the~~ IRB per institutional requirements. The recorded event 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

VIII.	Statistical Considerations D. Sample Size Approximately 40 subjects (20 with genetically-defined subtypes of PD and 20 ~~PD drug naïve~~ ***idiopathic PD*** subjects). Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker-responsive idiopathic PD subjects to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the same study protocol and outcome metrics.
IX	B. Packaging Labeling Each container is labeled with appropriate product information meeting current regulatory requirements, in compliance with 21 CFR 312.6 ***and Eudralex Vol. 4 EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13***
X.	Safety Management C9. Dose Modification Guidelines In the event that any patient develops elevated INR ≥ grade 2 in severity (> 1.5-2.5 x ULN) per CTCAE criteria version 4.0 thought to be related to treatment with EPI-743, administration of EPI-589 will be reduced by ~~1/3~~rd ***1/2*** to ~~66~~ ***50*** percent of the starting dose. Should the INR toxicity not resolve to at least grade 1 in severity within two weeks of the initial dose reduction, administration of EPI-589 may either be further reduced or discontinued. Once a patient's dose is reduced due to elevated INR thought to be related to study drug administration, their dose should not be re-escalated.

End of Document

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EPI589-15-002
A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects

Original Protocol:	27 April 2015
Protocol Amendment 1.0:	09 September 2015
Protocol Amendment 2.0:	04 January 2016

Edison Pharmaceuticals, Inc.
350 North Bernardo Avenue
Mountain View, CA 94043

Table of Contents

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PROTOCOL SYNOPSIS

Title of study	A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects
Protocol number	EPI589-15-002
IND number	126,795
EudraCT number	2015-001786-10
Original Protocol Date	27 April 2015
Protocol Amendment 1.0 Date	09 September 2015
Protocol Amendment 2.0 Date	04 January 2016
Investigative Drug	EPI-589
Study Sponsor	Edison Pharmaceuticals Inc. 350 North Bernardo Avenue Mountain View, CA 94043
Investigators and Investigative Sites	• [redacted] USA • [redacted] UK
Study population	Approximately 40 subjects with Parkinson's disease (PD) including 20 subjects with genetically-defined subtypes
Rationale for Study	<u>Mitochondrial pathophysiology</u> It is now well appreciated that defects in mitochondrial function contribute to the pathophysiology of PD both in subjects with defined genetic defects as well as those with idiopathic forms of the disease. <u>High morbidity</u> Despite the available therapies for symptomatic relief, PD remains a highly morbid disease. There are no approved treatments for PD capable of modifying disease progression. <u>Pre-clinical efficacy data</u> EPI-589 is a redox active molecule that has demonstrated potency (EC50 < 100nM) and efficacy (>80% rescue from oxidative stress-induced cell death)

	in cells derived from patients diagnosed with idiopathic and familial PD subtypes including PINK1, parkin and LRRK2.
Study objectives	Primary Objective To evaluate the effects of EPI-589 on safety as assessed by occurrence of drug-related serious adverse events in subjects with PD. Secondary Objectives To evaluate the effects of EPI-589 in subjects with PD on: 1. Glutathione cycle biomarkers as measured in blood, cerebral spinal fluid, and urine 2. Clinical disease state as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) 3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D 4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA) and 5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery and Asberg Depression rating scale (MADRS) 6. Pharmacokinetics 7. Hematology, blood chemistry, electrocardiogram
Study design	Open-label study with 30-day run-in phase.
Planned number of subjects	Approximately 40 subjects (20 with genetically-defined subtypes of PD and 20 drug-naïve idiopathic PD subjects). (Adaptive design component allows enrollment of up to 20 additional subjects with idiopathic PD to try to achieve a total of 20 subjects that have a biomarker response to EPI-589.)
Study duration	3 months (85 days ± 3 days) of study treatment preceded by a 1-month baseline parameter run-in period.
Test product, mode of administration, and dose	Test product EPI-589 in a tablet formulation at a strength of 250 mg

	Mode of Administration Oral with meal Dose EPI-589 500-mg BID
Reference therapy, dose, and mode of administration	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. Hoehn and Yahr stage ≤ 2.5 2. Ambulatory with or without assistance 3. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., hormonal methods, including oral, subcutaneous, and intrauterine; barrier methods, including [redacted] condom, [redacted] condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study treatment. 4. Willingness and ability to comply with study procedures 5. Stable regimen of dietary supplements for 30 days prior to enrollment 6. Abstention from use of other investigative or non-approved drugs for the duration of the trial *For Idiopathic Subjects* 7. *For idiopathic subjects*: a diagnosis of early idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a

dopaminergic deficit

8. *For idiopathic subjects*: must not yet require symptomatic medications for PD and not expected to require such treatment before the end of the study
9. *For idiopathic subjects:* age 40 to 75 years
10. *For idiopathic subjects*: within 5 years of diagnosis of Parkinson's disease

For Genetic Subtype Subjects

11. *For genetic subtype subjects*: a confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LARK2 or other mitochondrial genetic subtype
12. *For genetic subtype subjects*: age 21 to 75 years
13. *For genetic subtype subjects*: stable medication regimen of PD drugs for 30 days (except 60 days for rasagiline) prior to enrollment

Exclusion criteria

1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation
2. Use of antioxidant supplements, specifically vitamins E and C beyond the recommended daily allowance
3. Other Parkinsonian disorders
4. MoCA score of <24
5. Revised Hamilton Rating Scale for Depression ≥ 11
6. Parkinsonism due to drugs or toxins
7. Diagnosis of any other clinically significant neurologic disease that will confound the assessment of effect of study drug on disease progression
8. Malignancy within past two years
9. Pregnant or plans to become pregnant or breast feeding
10. History of stroke
11. History of brain surgery
12. Hepatic insufficiency with liver function tests

(LFTs) > 3 times upper limit of normal

13. Renal insufficiency as defined by creatinine > 1.5 times normal
14. End stage cardiac failure
15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD

For Idiopathic Subjects

16. *For idiopathic subjects*: use of any MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease for idiopathic subjects
17. *For idiopathic subjects*: use of nortriptyline or fluvoxamine 60 days prior to enrollment

Treatment

Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues. Post-treatment follow-up will be at least 10 days and up to 30 days after last dose.

Efficacy variables

1. Blood-based glutathione biomarkers
2. CNS biomarkers
3. Urine-based biomarkers
4. MDS-UPDRS
5. Non-motor Symptoms Scale (NMSS)
6. PDQ-39
7. EQ-5D
8. MoCA
9. Beck Depression Inventory (BDI)
10. Montgomery & Asberg Depression rating scale (MADRS)
11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)
12. Pharmacokinetics

Safety variables	Clinical 1. Routine assessments of AEs and SAEs 2. Dose limiting toxicities 3. Electrocardiogram 4. C-SSRS 5. Laboratory 6. Routine serum chemistries with liver function tests 7. Routine hematology tests with coagulation tests
Statistical Considerations	Data Analysis This is a within-subject, controlled open-label study seeking to determine the safety and tolerability of EPI-589 in patients with PD as well as to determine if EPI-589 can alter the biochemical signature of PD as assessed by peripheral blood biomarkers, CNS biomarkers, brain imaging biomarkers, and urine biomarker analysis. In addition, data on a number of disease-relevant clinical measures will be collected.

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I. SCHEDULE OF ASSESSMENTS AND DOSING SCHEDULE

Tests	-2 to -1 Months		Day 0	Month 1	Month 2	Month 3 End of Treatment Visit	Post-Treatment Follow-up
	Screening	Run-in (± 30 days)	Baseline	Day 29 (± 3 days)	Day 57[d] (± 3 days)	Day 85 (± 3 days)	Up to 30 Days after Last Dose[e]
Informed consent	✓						
Inclusion/Exclusion criteria	✓						
Past Medical history	✓						
Previous genetic testing review	✓						
Physical exam & Vital signs	✓		✓	✓		✓	
Height & weight	✓		✓[a]	✓		✓	
12-lead ECG	✓		✓[a]	✓		✓	
Hematology (including coagulation panel)	✓		✓[a]	✓		✓	
Serum Chemistry	✓		✓[a]	✓		✓	
Pregnancy test[b]	✓		✓	✓		✓	
C-SSRS			✓	✓		✓	
Montreal Cognitive Assessment	✓					✓	
DaTscan	✓						
Revised Hamilton Rating Scale for Depression	✓						
Subject enrolls in study		X					
Blood-based glutathione cycle biomarkers		✓	✓	✓		✓	
Lumbar puncture (CNS biomarkers)		✓				✓	
Urine-based biomarkers		✓	✓	✓		✓	
MDS-UPDRS		✓	✓	✓		✓	
Timed motor tests (for subjects on dopamine therapy)		✓	✓			✓	
NMSS, PDQ-39, EQ-5D			✓			✓	
BDI, MADRS			✓			✓	
Drug plasma concentration[c]				✓[c]		✓[c]	
AE/SAE assessment[d]				✓	✓[d]	✓[d]	✓[e]
Concomitant medications assessment	✓	✓	✓	✓	✓[d]	✓[d]	✓[e]
Post-Treatment Assessments[e]							✓[e]

a. Screening values can be used if done within one month of baseline.
b. Female subjects of childbearing potential must have a negative pregnancy test.
c. Full plasma concentration profile will be obtained at Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing from the first 10 subjects to complete 1 month of therapy at each site.
d. Month 2 assessments can be done by telephone. Any new AEs and associated concomitant medications reported at Month 3 must be followed for 30 days; this follow up may be conducted by telephone.
e. AE/SAE and concomitant medication assessments conducted by telephone at least 10 days after last dose. Additional assessments determined at Investigator discretion.

Dosing Schedule				Month 1	Month 2	Month 3	Post-Treatment
EPI-589 500-mg BID				✓	✓	✓	

II. INTRODUCTION

A. Background Information and Rationale

Parkinson's disease (PD) is a highly morbid neurodegenerative movement disorder that has a number of neuromuscular, cognitive and neuropsychiatric manifestations as well as non-neurological symptoms. PD is the second most common neurodegenerative disorder with an estimated prevalence of 6.3 million people worldwide (EPDA).

PD has long been considered a non-genetic (idiopathic) disease; however, about 5% of patients have an identifiable mutation. Disease onset typically occurs after age 50, however, in a subset of patients, disease onset can occur at a younger age. The primary motor symptoms result from death of dopamine-producing cells in the pars compacta region of the substantia nigra. However, the mechanisms underlying this cell death and disease pathology remain poorly understood. There is no approved treatment for PD capable of modifying disease progression. Current therapies partially address disease motor symptoms through levodopa or dopamine agonists or other agents, and other disease symptoms (e.g. neuropsychiatric symptoms), but disability tends to increase over time despite these treatments.

The association of PD with mitochondrial pathology and high levels of oxidative stress are well established. Increased levels of oxidative stress have been consistently measured in post-mortem specimens from PD patients (Maarouf 2012, Reale 2012). The occurrence of PD-like symptoms in heroin addicts exposed to MPTP in the 1980s established a first link between PD and mitochondrial injury (Langston 1983, Dauer and Przedborski 2003). MPTP inhibits complex 1 of the mitochondrial respiratory chain and induces degeneration of dopaminergic cells through oxidative stress-mediated injury. The link between mitochondrial injury and PD was further strengthened by the induction of PD symptoms following exposure to another neurotoxic complex 1 inhibitor, rotenone (Betarbet et al 2000, Greenamyre et al. 2003), which like MPTP has come to be used in pre-clinical testing for its phenotypic similarities to PD.

Furthermore, the identification of genetic mutations such as PINK1, parkin, LRRK2 and others in mitochondrial genes in familial PD patients provided the strongest link between the mitochondria and PD (Winklhofer and Haass 2010). Normally these genes influence oxidative balance and provide neural protection of the dopaminergic neurons that are affected by PD. PINK1 and parkin are involved in protecting against oxidative stress (OS) and overabundant reactive oxygen species (ROS), and are implicated in cell morphology and dynamics, as well as in the preferential degradation of dysfunctional mitochondria or "mitophagy" (Ashrafi et al. 2014). Mutant LRRK2 leads to the accumulation of misfolding intracellular protein accumulations, cell stress and apoptosis (Giasson et al. 2006, Zhu et al. 2006).

The importance of oxidative stress in PD pathology is further substantiated by the measurement of decreased levels of reduced glutathione in the brains of patients with PD (Holmay et al. 2013). Glutathione levels are low at very early stages of PD and correlate with disease severity (Riederer et al. 1989), and experimental induction of glutathione depletion leads to mitochondrial complex I dysfunction (Jha et al, 2000;). Reduced glutathione is an essential intermediary

metabolite that serves as the primary native cellular antioxidant. In a state of high oxidative stress, elevated levels of ROS outstrip the supply of glutathione (GSH) resulting in depletion of GSH and ROS-mediated cell death.

Given the important role of oxidative stress and mitochondrial pathology in PD, a redox-active therapy that could target key pathways in cellular OS response pathways may hold promise for the treatment of PD.

B. Rationale for the Study of EPI-589 in Parkinson's Disease

EPI-589 is a redox active molecule that has demonstrated potency (EC50 <100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with idiopathic and familial PD genetic subtypes including PINK1, parkin and LRRK2.

In these cell-based assays, primary fibroblasts from patients (and control) were pre-incubated with and without test compound, then treated with L-buthionine-(S,R)-sulfoximine (BSO), a GSH synthesis inhibitor, to initiate depletion of cellular GSH. GSH depletion has been shown to lead to OS and disruption of calcium homeostasis resulting in loss of the mitochondrial membrane potential and cell death. Under these conditions, the control cells are resistant to the stress and the fibroblast cells from patients with disease indications die within 36 to 48 hours. Pretreatment of cells with EPI-589 prior to initiation of GSH depletion potently protected against oxidative stress-mediated cell death, with EC_{50} response concentrations of 16 to 52 nM. (Table 1).

Table 1: Cell Line Rescue with EPI-589 in Parkinson's Disease Genetic Subtypes

	EPI-589 **EC_{50} (nM range)**
PINK1	26-36
LRRK2	16-18
parkin	42-52

C. Name and Description of Investigational Product

The IUPAC name of 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 derived from resolved (R)-Trolox®, a derivative of vitamin E in the form of a pale yellow to yellow solid. The EPI-589 drug product will be provided in a 250-mg tablet formulation.

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. In 28-day and 91-day repeat-dose toxicity studies in rat and cynomolgus monkey, the no observed adverse effect level (NOAEL) was 300 mg/kg/day, corresponding to combined mean Cmax values of 37,717 to 56,500 ng/mL (rat) and 14,300 to 16,417 ng/mL (monkey), and a combined mean area under the plasma concentration-time curve from time zero to the last measurable concentration (AUClast) value of 149,495 to 297,000 ng.h/mL (rat) and 47,300 to 67,656 ng.h/mL (monkey) (Studies 1660-038, 1660-039, 1660-063, and 1660-064).

A phase 1 clinical study demonstrated that healthy subjects administered 500 mg EPI-589 BID for 14 days showed a mean Cmax value of 1,890 ng/mL and a mean AUClast value of 5,240 ng.h/mL (Study EPI589-14-01). These plasma concentrations are well below the mean exposure values in monkey associated with the NOAEL in the toxicity studies, corresponding to safety margins of approximately 7- to 8-fold for the mean Cmax and 9- to 12-fold for the mean AUC.

During the 28-day repeat-dose toxicity studies, rat and monkey were exposed to up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-039 and 1660-038). The NOAEL for both studies was 300 mg/kg/day. Rats exposed to 1,000 mg/kg/day exhibited adverse 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 showing corresponding microscopic pathology. The majority of these findings were resolved following the 28-day recovery period. Monkeys exposed to 1,000 mg/kg/day showed significant test-article related morbundity that resulted in half the animals in the high dose group being euthanized on Days 3 and 4 and the remaining animals being euthanized on Day 9. These animals exhibited significant elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values, and microscopic findings in the kidney, liver, skeletal muscle, heart, and lymphoid tissues. In several of the animals the primary cause of morbidity was determined to be test-article related renal tubular degeneration/necrosis.

During the 91-day repeat-dose toxicity studies, rat and monkey were exposed to up to 300 mg/kg/day EPI-589 PO (Studies 1660-063 and 1660-064). The NOAEL for the rat study was 300 mg/kg/day and the no observed effect level (NOEL) for the monkey study was 300 mg/kg/day. [redacted] rats exposed to 300 mg/kg/day and [redacted] rats exposed to ≥ 100 mg/kg/day exhibited mild test-article related effects on hematology parameters consistent with hemolysis and bone marrow regeneration. These findings were not considered adverse.

Development and reproductive toxicology studies were conducted in rat and rabbit at doses up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-069, 1660-067, and 1660-068). The NOAEL for reproductive toxicity in rat was demonstrated to be 1,000 mg/kg/day (1660-069). The NOAEL

for developmental toxicity in rat and rabbit during the embryofetal studies was deemed to be 300 mg/kg/day (Studies 1660-067 and 1660-068). Rats exposed to 1,000 mg/kg/day exhibited 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. Rabbits exposed to 1,000 mg/kg/day exhibited 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 (Study EPI589-14-01) and rabbits exposed to 1,000 and 300 mg/kg/day EPI-589 is approximately 179- to 236-fold and 47- to 50-fold, respectively. 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 (Study AD58AS.502ICH.BTL); 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 (Study AD58AS.331ICH.BTL); and negative in the in vivo micronucleus assay in rat (Study AD58AS.125012ICH.BTL). These data indicate a low clinical mutagenicity risk.

Primary pharmacodynamics studies demonstrated that EPI-589 is a potent rescue agent in cellular models of diseases of energy metabolism and oxidative stress. In vitro cellular models utilizing primary human fibroblasts from patients with ALS, Parkinson's disease and other diseases characterized by high levels of oxidative stress, or striatal cells derived from mouse models of Huntingdon's disease were used to assess the potential of EPI-589 to mitigate the harmful effects of oxidative stress (Studies EPI-BA-000216, EPI-BA-000363, and EPI-BA-000362). Pretreatment of patient cells with EPI-589 potently protected against oxidative stress-mediated cell death in a concentration dependent manner. Furthermore, EPI-589 normalized 3-nitrosotyrosine (3NT) levels, a biomarker of oxidative stress, and increased glutathione levels in mouse striatal cells under oxidative stress conditions.

In secondary pharmacodynamics in vitro receptor/ion channel binding studies, EPI-589 did not significantly affect off-target molecular targets (Study EPI-BA-159). In safety pharmacology studies, EPI-589 did not significantly affect ion channel current in the hERG assay (Study 130719.FEK); did not affect ECG parameters during the 28-day and 3-month repeat-dose toxicology studies in monkey at doses up to 1,000 mg/kg/day (only Day 1 data collected for animals administered 1,000 mg/kg/day and up to Day 91 data collected for animals administered up to 300 mg/kg/day) (Studies 1660-038 and 1660-064); and did not change respiratory function or adversely impact neurobehavioral function in rat at doses up to 1,000 mg/kg (Studies 1660-051, 1660-050, and 1660-063).

In single dose exposure PK studies, EPI-589 was absorbed rapidly in rat, dog, and monkey, with mean T_{max} values ranging from .08 to 1 hour and mean T1/2 values ranging from 3.7 to 5.0 hours (Studies EPI-BA-53, EPI-BA-59, EPI-BA-72, and EPI-BA-302). EPI-589 does not significantly induce cytochrome P450 (CYP) enzymes and appears to be metabolized by reductases in the

liver cytosol and microsomal subcellular fractions and to a lesser extent by the family of CYP enzymes (Studies MC12M-0037 and MC14M-0018).

EPI-589 exhibited weak direct inhibition of CYP2B6, CYP2C8, CYP2C9, and CYP3A4/5 (both midazolam and testosterone as probe substrates) with estimated IC_{50} (μM) values and R values based on free plasma concentrations (shown in parentheses) of 28 (1.25), 40 (1.18), 92 (1.08), 34 (1.21), and 53 (1.13), respectively (Study MC14M-0020)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.

D2. Clinical Studies

Phase I Study EPI589-13-022 evaluated the pharmacokinetics, safety and tolerability of single ascending oral doses (SADs) of EPI-589 in healthy subjects and a preliminary evaluation of safety and tolerability data was performed. Sixteen AEs were reported in the 36 subjects who received administration of EPI-589. Ten subjects (27.8%) who received EPI-589 (and 2 subjects, 20% on placebo) reported AEs that were assessed as related. All were mild and resolved during the study, with the exception of a common cold (1 subject) and cold sore (1 subject). 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. Twenty-six subjects (65.0%) on EPI-589, and 8 subjects (80%) on placebo reported AEs. Twenty-four of 34 AEs were considered by the Investigator to be related to EPI-589. Nineteen subjects (47.5%) on EPI-589, and 6 subjects (60%) on placebo reported AEs that were assessed as related. All adverse events were mild, except for 1 AE which was moderate (unrelated brain contusion). All AEs were resolved during the study, with the exception of one, which was a common cold. 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 the MAD study it may be concluded that there is no objection to proceed with treatment with 250-mg, or 500-mg doses of EPI-589.

E. Human Pharmacokinetics

EPI-589 was fast absorbed following oral administration in SAD Study EPI589-13-022. The median C_{max} was attained approximately within 1 hour under fasted conditions after dosing. The median T_{max} values were attained in 0.50 to 1.00 hours over the dose range of 50 to 1000 mg under fasted conditions and 3.01 hours at the 500 mg dose level under fed conditions. Mean half-life ranged from 5.55 to 10.7 hours over the dose range of 50 to 1000 mg under fasted conditions and 4.91 hours at the 500 mg dose level under fed conditions. Half-life was independent of the dose levels over the dose range of 50 to 1000 mg under fasted conditions. The rate of EPI-589 absorption, as measured by C_{max}, was decreased by 24.07% under fed conditions at the 500 mg

dose level. The extent of absorption as measured by AUCs (AUC_{0-t} or AUC_{0-inf}) was not affected under fed conditions in the 500 mg dose groups.

In MAD study EPI589-14-01, 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 of various ages and smoking status. No significant effects of age or smoking on EPI-589 pharmacokinetics were observed in this study. Dose proportionality existed in the exposures (AUC_{0-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

EPI589-15-002: A Phase 2A Safety and Biomarker Study of EPI-589 in in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects.

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 meals.

H. Compliance Statement

This study will be conducted in full accordance with all applicable research policies and procedures, the EU Clinical Trials Directive, all applicable EU and 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, will obtain consent and will 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.

I. Relevant Literature and Data

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

III. STUDY OBJECTIVES

A. Primary Objective

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 PD.

B. Secondary Objectives

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

1. Glutathione cycle biomarkers as measured in blood, cerebral spinal fluid, and urine
2. Clinical disease state as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D
4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA)
5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery & Asberg Depression rating scale (MADRS)
6. Pharmacokinetics
7. Hematology, blood chemistry, electrocardiogram

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IV. INVESTIGATIONAL PLAN

A. General Schema of Study Design

Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues.

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects. Given that the investigational drug targets an enzyme key to glutathione synthesis and that glutathione depletion has been found to be associated with PD, we are seeking to determine the safety and potential biochemical benefit of EPI-589 in PD subjects as assessed by glutathione cycle biomarkers. If we determine that there are a subset of subjects with normal levels of glutathione who do not demonstrate biochemical changes following drug administration, and a subset of subjects with low levels of reduced glutathione who do respond to drug treatment, we would seek to enroll additional idiopathic PD subjects with low glutathione levels to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the study outcome metrics. EPI-589 will be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues.

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 run-in scans, CNS, blood-based biomarker, urine-based biomarker and clinical measurements will be collected.

A3. Baseline

Baseline assessments, scans, blood-based biomarker, urine biomarker, 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-based biomarker, urine biomarker, and clinical measurements will be collected at Day 29 (± 3 days) and Day 85 (± 3 days).

A5. End of Treatment

End of treatment data will be collected at the last study visit Day 85 (± 3 days).

AEs reported as ongoing at Day 85 (± 3 days) and/or any concomitant medications associated with such events 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.

A6. Post-Treatment Follow-up

Post-Treatment Follow-up will be at least 10 days and up to 30 days after last dose: AE/SAE and concomitant medication assessments conducted by telephone. Additional assessments to be determined at Investigator discretion.

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 biomarker and clinical baseline measurements. EPI-589 will then be administered for 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues. A post-treatment follow-up will be conducted up to 30 days after last dose.

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

This study will be conducted at two study sites:

- [redacted] UK
- [redacted] USA.

Approximately 40 subjects with PD are projected:

- 20 with genetically-defined subtypes
- 20 PD drug-naïve

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the same study protocol and outcome metrics.

D. Study Population

D1. Inclusion Criteria

1. Hoehn and Yahr stage ≤ 2.5
2. Ambulatory with or without assistance
3. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., hormonal methods, including oral, subcutaneous, and intrauterine; barrier methods, including [redacted] condom, [redacted] condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study treatment.
4. Willingness and ability to comply with study procedures
5. Stable regimen of dietary supplements for 30 days prior to enrollment
6. Abstention from use of other investigative or non-approved drugs for the duration of the trial

For Idiopathic Subjects

7. *For idiopathic subjects*: a diagnosis of early idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit
8. *For idiopathic subjects*: must not yet require symptomatic medications for PD and not expected to require such treatment before the end of the study
9. *For idiopathic subjects*: age 40 to 75 years
10. *For idiopathic subjects*: within 5 years of diagnosis of Parkinson's disease

For Genetic Subtype Subjects

11. *For genetic subtype subjects*: a confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LARK2 or other mitochondrial genetic subtype
12. *For genetic subtype subjects*: age 21 to 75 years
13. *For genetic subtype subjects*: stable medication regimen of PD drugs for 30 days (except 60 days for rasagiline) prior to enrollment

D2. Exclusion Criteria

1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation
2. Use of antioxidant supplements, specifically vitamins E and C beyond the recommended daily allowance
3. Other Parkinsonian disorders
4. MoCA score of <24
5. Revised Hamilton Rating Scale for Depression ≥ 11
6. Parkinsonism due to drugs or toxins
7. Diagnosis of any other clinically significant neurologic disease that will confound the assessment of effect of study drug on disease progression
8. Malignancy within past two years

9. Pregnant or plans to become pregnant or breast feeding
10. History of stroke
11. History of brain surgery
12. Hepatic insufficiency with liver function tests (LFTs) > 3 times upper limit of normal
13. Renal insufficiency as defined by creatinine > 1.5 times normal
14. End stage cardiac failure
15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD

For Idiopathic Subjects

16. *For idiopathic subjects*: use of any MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease for idiopathic subjects
17. *For idiopathic subjects*: use of nortriptyline or fluvoxamine 60 days prior to enrollment

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V. STUDY PROCEDURES

A. Screening Visit

Screening evaluations will be performed within two months of first dose. The Investigator will inform each prospective subject of the nature of the study, explain the potential risks, and must 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. Receipt and review of previous testing including genetic tests
4. Physical examination including vital signs
5. Height and weight
6. 12-lead ECG
7. Laboratory assessments for hematology, coagulation, and serum chemistry (See Sections VI.D3.a and VI.D3.b)
8. Urine pregnancy test (women of childbearing potential must have a negative urine pregnancy test; see Section VI.D3.c)
9. MoCA
10. DaTscan
11. Revised Hamilton Rating Scale for Depression
12. Concomitant medications assessment (last 60 days prior to enrollment)

A1. Run-in Assessments

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 within one month for Run-in assessments. These will 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. Blood-based glutathione cycle biomarkers
2. CNS biomarkers (lumbar puncture)
3. Urine biomarkers
4. MDS-UPDRS
5. Timed motor tests (for subjects on dopamine therapy)
6. Concomitant medications review

B. Treatment Phase

After the Run-in phase, the subject must return to the clinic within 30 days (± 3 days) for baseline assessments. In-clinic study visits are scheduled at Month 1 and Month 3. The Month 2 study assessments can be conducted via telephone. End of treatment assessments will be conducted 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 including vital signs
2. Height and weight*
3. 12-Lead ECG*
4. Blood-based GSH cycle biomarkers
5. Urine-based biomarkers
6. Laboratory assessments for hematology, coagulation and serum chemistry*
7. Urine pregnancy test (females of child bearing potential)
8. C-SSRS (Columbia Suicide Severity Rating Scale)
9. MDS-UPDRS
10. NMSS, PDQ-39, EQ-5D
11. BDI, MADRS
12. Timed motor tests (for subjects on dopamine therapy)
13. Concomitant medications review

* Screening results for these assessments may be used if obtained within 1 month of Baseline.

B2. Study Visit Assessments

- Month 1 Clinic Visit (Day 29 ± 3 days):

The following will be assessed or performed at the Month 1 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry
5. Urine pregnancy test (females of child bearing potential)
6. C-SSRS
7. Blood-based GSH cycle biomarkers
8. Urine-based biomarkers
9. MDS-UPDRS
10. Pharmacokinetics: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.
11. AE assessments
12. Concomitant medications review

- Month 2 Visit (Day 57 ± 3 days)

Month 2 assessments can be conducted by telephone and must include review of:

1. Concomitant medication
2. AEs

- Month 3 Clinic Visit (Day 85 ± 3 days)

The following will be assessed or performed at the Month 3 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry
5. Urine pregnancy test (females of child bearing potential)
6. C-SSRS
7. Blood-based GSH cycle biomarkers
8. Urine-based biomarkers
9. CNS biomarkers
10. MDS-UPDRS
11. Pharmacokinetics: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.
12. AE assessments
13. Concomitant medications review
14. MoCA
15. NMSS, PDQ-39, EQ-5D
16. BDI, MADRS
17. Timed motor tests (for subjects on dopamine therapy)

B3. Pharmacokinetics

Plasma concentration samples will be collected from the first 10 subjects to complete 1 month of therapy at each site, at the following time points:

- Month 1 (Day 29 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose
- Month 3 (Day 85 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose

B4. Early Termination Study Visit

Subjects who terminate from the study after receiving first dose and prior to the completion of all scheduled visits should have the end of treatment visit assessments completed as soon as possible.

C. End of Treatment Visit

End of treatment visit takes place at Month 3 (Day 85 ± 3 days) and includes the assessments listed in Section VB2 Study Visit Assessments.

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. Post-Treatment Follow-up

Post-Treatment Follow-up will be at least 10 days and up to 30 days after last dose, with AE/SAE and concomitant medication assessments conducted by telephone. Additional assessments to be determined at Investigator discretion.

E. Unscheduled Visits

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

F. Concomitant Medication

Any medication taken by a subject ≤ 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 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 consulting the Investigator.

G. 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 and for the duration of the study in a trial of a device, drug or other therapy for PD
3. Use of MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease for idiopathic subjects
4. Use of nortriptyline or fluvoxamine

H. Subject Withdrawals

Subjects receive study treatment until treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The following conditions require subject discontinuation from all study treatment:

1. At their own request or at the request of their legally authorized representative
2. If a subject experiences a serious or severe adverse event that is deemed related to treatment with EPI-589 and in the Investigator's or the Sponsor's medical judgment continuation of treatment would be detrimental to the subject.
3. At the specific request of a regulatory agency for termination of treatment of an individual subject or all subjects under the protocol

4. Subject participation in another clinical study using an investigational agent or investigational medical device
5. Use of prohibited medications such as vitamins E and C beyond the recommended daily allowance; nortriptyline or fluvoxamine; and, for idiopathic subjects, MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease
6. Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use medically accepted methods of contraception
7. If a subject becomes pregnant.
8. Significant noncompliance with the protocol in the opinion of the Investigator or the Sponsor

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 IX.B.

Evaluations should 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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VI. 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 PD.

B. Secondary Endpoints (Efficacy)

1. Blood-based biomarkers
2. CNS-based biomarkers
3. Urine-based biomarkers
4. MDS-UPDRS
5. NMSS
6. PDQ-39
7. EQ-5D
8. MoCA
9. BDI
10. MADRS
11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)
12. Pharmacokinetics

C. Secondary Endpoints (Safety)

1. Routine assessments of AEs and SAEs
2. Dose limiting toxicities
3. Routine serum chemistries with liver function tests
4. C-SSRS
5. Routine hematology tests with coagulation tests
6. Electrocardiogram

D. Screening and Baseline Evaluation

D1. Physical Examination

Complete physical exams will be conducted (excluding genital/rectal exam) at protocol specified study visits. 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, heart, abdomen, and extremities.

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).

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

D2. Height and Weight

Weight (kg) will be measured in ordinary indoor clothing (i.e., street clothes, scrubs, etc.) with shoes off. Height will be recorded in centimeters (cm).

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.

D3. Laboratory Evaluations

Subjects 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 I).

a. 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 (WBC) 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) with INR, partial thromboplastin time (PTT), activated (aPTT)

b. Serum chemistry

1. Liver: Alkaline Phosphatase (ALP), ALT (serum glutamic-pyruvic transaminase [SGPT]), AST (serum glutamic-oxaloacetic transaminase [SGOT]), bilirubin (total and direct), gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH)
2. Renal: blood urea nitrogen (BUN), and creatinine
3. Electrolytes: sodium, potassium, chloride, and carbon dioxide (CO2) as bicarbonate
4. General: creatine phosphokinase (CPK), creatine kinase (CK), and troponin (at baseline only); total protein, 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

c. Urine pregnancy test

1. Human chorionic gonadotropin (HCG) beta subunit will be measured on all female subjects of childbearing potential.

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.

Diagnoses associated with any NIH Common Terminology Criteria for Adverse Events (CTC v4.03) Grade 3 or 4 laboratory abnormalities will be recorded as SAEs on the CRF. Repeated and verified ≥ Grade 3 laboratory tests will be reported as an SAE to the Sponsor and the IRB per institutional requirements. The recorded event 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.

D4. 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.

E. Sample Collection Procedures, Bioanalytical Methods and Sample Shipment

Subject samples will be identified by unique sample codes.

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

F. Efficacy Evaluations

F1. Glutathione Cycle Biomarkers

Blood, urine, and CNS levels of oxidized and reduced GSH as well as GSH metabolites will be used to evaluate EPI-589 target engagement and ability to correct a key biochemical aspect of disease pathology.

F2. Parkinson's Disease Rating (MDS-UPDRS)

The MDS-UPDRS is a tool for monitoring the impact of PD, the degree of disability caused, and complications from treatment. Part I evaluates nonmotor experiences of daily living; Part II evaluates motor experiences of daily living; Part III is a motor examination and includes the Hoehn and Yahr scale; Part IV examines motor complications (e.g., motor fluctuations and dyskinesias).

Several questions from Part I and all questions from Part II are designed to be amenable to a patient/caregiver questionnaire format; the remaining interview (Part I and Part III) and

examination (Part IV) are designed with the expectation they can be completed within 30 minutes. Each item is measured on a five-point scale.

F3. Non-motor Symptoms (NMSS)

Non-motor symptoms are evaluated using the NMSS which is divided into 30 questions in 9 different domains including such symptoms as dribbling saliva, constipation, depression, sleep disorders, apathy, hallucinations and dementia. Symptoms are quantified based on their severity (using a scale of 0 to 3) and frequency (using a scale of 0 to 4). The final cumulative scores are derived from adding up the product of the frequency score times severity score for each of the 30 questions.

F4. Parkinson's Disease Questionnaire (PDQ-39)

PDQ-39 is a self-administered questionnaire for patients with PD that has 39 questions relating to eight key areas of health and daily activities, including both motor and non-motor symptoms. It is scored on a scale of 0 to 100, with lower scores indicating better health, and high scores more severe symptoms.

F5. EQ-5D

EQ-5D is a questionnaire designed to provide measures of health-related quality of life states, consisting in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

F6. Montreal Cognitive Assessment (MoCA)

MoCA is a 30-point questionnaire for cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Severity ranges are approximately: 26 to 30 normal; 18 to 26 mild cognitive impairment; 10-17 moderate cognitive impairment; < 10 severe cognitive impairment.

F7. Beck Depression Inventory (BDI)

The BDI is a self-reporting inventory that measures characteristic attitudes and symptoms of depression, including physical symptoms. Twenty-one questions have four responses each (rated 0 to 3) with a total cumulative score scale ranging from 1-10 considered normal) > 40 (extreme depression).

F8. Montgomery and Asberg Depression rating scale (MADRS)

The MADRS is a clinician-rated tool for measuring changes in depressive symptom severity. Ten core symptoms and cognitive features are rated on a severity scale of 0 to 6. Higher scores indicate increasing depressive symptoms.

F9. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)

Timed motor tests are simple, objective, quantitative measures for the assessment of Parkinson's disease. They include, in an on-medication and an off-medication state, timed recorded physical movements.

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VII. 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.

A1. Analysis Populations

Demographic characteristics and baseline efficacy data will be presented and summarized by treatment group for all subjects in the efficacy intent to treat (EITT) population. Demographic information will also be summarized by treatment group 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. CNS biomarkers
3. Urine-based biomarkers
4. MDS-UPDRS
5. NMSS
6. PDQ-39
7. EQ-5D
8. MoCA
9. BDI
10. MADRS
11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)
12. Pharmacokinetics

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 PD.

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 40 subjects (20 with genetically-defined subtypes of PD and 20 PD drug-naïve subjects). Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker-responsive idiopathic PD subjects to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the same study protocol and outcome metrics.

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VIII. STUDY MEDICATION

A. Description

EPI-589 is presented as an immediate release film-coated tablet. Each tablet contains 250 mg of EPI-589 and the following compendial excipients: lactose, 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, in compliance 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 HPDE 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]).

C. 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 verification with subject-completed diary cards and returned used drug supply.

D. Drug Accountability

Dosing information will be captured on a subject Dosing Diary Form. This form is part of the 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 Investigator study file to assure the study medication is 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 either be 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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IX. 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 in accordance with the IRB policies and as detailed below. AEs that are not serious will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

B1. Safety Guidance

Based on the known clinical manifestations of Parkinson's disease, we expect that many AEs could occur during the course of the trial that are well documented to occur as the results of the natural history of this disease. These include, but are not limited to worsening neuromuscular function, depression, decline in cognitive function, loss of vision and other ophthalmological symptoms, loss of coordination and loss of speech.

As there are no data available regarding EPI-589 phototoxicity, investigators are to advise subjects to take measures to minimize exposure to ultraviolet (UV) light for the duration of the study and for one week after the last dose.

Edison Pharmaceuticals 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, Edison Pharmaceuticals should be provided with a copy of any post-mortem findings, including histopathology.

C. Definition of an Adverse Event

C1. Adverse Event

An 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" or "AE".

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)

An 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; or
5. A congenital anomaly/birth defect.

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 subject 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 an SAE which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether other AEs, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject, require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

[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; follow-up of the pregnancy, fetus, and child will continue for at least 8 weeks after delivery. While pregnancy itself is not considered an

AE or SAE, all pregnancies should be reported using the same process as for SAEs. Any pregnancy complications or an outcome other than a healthy, normal outcome will be recorded as an AE or SAE.

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.

C3. Non-serious Adverse Event

A non-serious AE 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 and reappears with re-introduction 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 indicated.

Grade 2 – Moderate limitation in activity, some assistance may be needed; minimal noninvasive medical intervention/therapy indicated.

Grade 3 – Severe limitation in activity, assistance usually required; medical intervention/therapy required; hospitalization or prolongation of hospitalization indicated; disabling.

Grade 4 – Extreme limitation in activity, significant assistance required; urgent medical intervention/therapy required; life-threatening consequences.

Grade 5 – Death

C6. Definition of Unexpected Adverse Event

Any AE, the specificity or severity of which is not consistent with those listed in the current investigator's brochure is considered "unexpected."

C7. Notification of SAEs

The Investigator is responsible for promptly notifying the IRB/IEC of all study on-site SAEs 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 MedWatch or CIOMs form (as appropriate).

SAEs (whether unexpected or expected AEs) must be documented on the designated SAE form. The SAE must be reported to the medical expert and appropriate Edison or Edison-assigned pharmacovigilance staff within 24 hours, according to regulatory, Sponsor, or ICH-E6 Good Clinical Practice, followed by the SAE form within two 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 Investigator and/or Medical Expert must also inform the Study Monitor and the Sponsor in all cases. Any SAEs must also be reported to the IRB/IEC. The Sponsor or designee will ensure that all legal reporting requirements are met.

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 a follow-up SAE forms.

The instructions to sites for the completion of SAE reports give detailed guidance on the reporting of SAEs and AEs initially reported as non-serious that become serious. When a non-

serious event becomes serious, details must be forwarded immediately to the Medical expert and Edison or Edison-assigned 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 reported to the relevant competent authorities.

In the US, all fatal or life-threatening suspected unexpected serious adverse events assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA as soon as possible (i.e., by telephone or facsimile transmission), but no later than 7 calendar days after first knowledge by the Sponsor that a report qualifies as a suspected unexpected fatal or life-threatening reaction. All unexpected serious adverse events, other than fatal or life-threatening, assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA within 15 calendar days from the day the Sponsor determines that the information qualifies as a SUSAR.

In the UK, the Sponsor or trial investigator must act immediately or at least within 24 hours after becoming aware of a SUSAR by informing the MHRA's Clinical Trial Unit by telephone. The MHRA must then be informed in writing within 3 days of the incident. All SUSARs originating in the UK or originating outside the UK involving the same medicinal product are to be reported. Fatal or life-threatening SUSARs are to be reported as soon as possible, but no later than after 7 days. Any additional relevant information must be sent within 8 days of the report. Non-fatal or non-life-threatening SUSARs are to be reported as soon as possible but no later than 15 days after becoming aware of the reaction.

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. All SAEs should be followed until either resolved or stable.

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 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.

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X. 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 Edison 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 Edison. 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 Edison 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 (0.001%), a systematic review of the database will be undertaken and corrections will be made to achieve an error rate of less than 0.001%.

AEs will be coded using MedDRA, version (14.3). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary, March 2014.

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 or 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, and the General Data Protection Regulation (GDPR).

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 EPI-589-14-01 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 PD. Therefore, we cannot assure that subjects will benefit from treatment with EPI-589. Potential benefits may manifest in a variety of ways, such as in disease-related parameters, functioning, and quality of life.

G3. Risk-Benefit Assessment

There are no effective and/or approved disease modifying treatments available for PD, 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 hold benefit for patients with PD. This is the first study to better understand EPI-589 target engagement and potential therapeutic

benefit in subjects with PD. 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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XI. PUBLICATION

A. Use of Study Results

All information concerning the product, as well as any matter concerning the operation of Edison (such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by Edison and are unpublished), are confidential and must remain the sole property of Edison. 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 Edison 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 Edison. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

This Study is part of a multicenter clinical research study. Accordingly, 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 while this Study is being conducted at other center/s. Only after the completion of this Study at all other centers, provision of the data to the FDA or EMA for review and comment, and publishing the combined data from all of the centers, may the Principal Investigator 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 Edison, Edison will allow the Investigator or CRO 60 days for full review of the manuscript before publication.

XII. LIST OF ABBREVIATIONS

AE	adverse event
AI	accumulation index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AR	accumulation ratio
BDI	Beck Depression Inventory
BID	twice daily
BSO	L-buthionine-(S,R)-sulfoximine
C-SSRS	Columbia-Suicide Severity Rating Scale
CBC	complete blood count
CFR	Code of Federal Regulations
CK	creatinine kinase
CNS	central nervous system
CoQ10	Coenzyme Q 10
CRF	Case Report Form
CRO	Contract Research Organization
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DaT	dopamine transporters
DSMB	data safety monitoring board
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EITT	efficacy intent-to-treat
EPDA	European Parkinson's Disease Association
EU	European Union
%F	percent fluctuation
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GCRC	good clinical research practice
GDPR	General Data Protection Regulation
GSH	glutathione
GSSG	glutathione disulfide
HDPE	high density polyethylene
hERG	human Ether-a-go-go Related Gene
HCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HMPAO	hexamethylpropylene amine oxime
ICF	informed consent form
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUPAC	International Union of Pure and Applied Chemistry

kg	kilogram
λz	apparent terminal constant
LFT	liver function test
MAD	multiple ascending (oral) dose
MADRS	Montgomery and Asberg Depression rating scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
mg	milligram
mL	milliliter
MoCA	Montreal Cognitive Assessment
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPV	mean platelet volume
mtDNA	mitochondrial DNA
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NF	National Formulary
nM	nanomolar
NMSS	Non-motor Symptoms Scale
NOAEL	no observed adverse effect level
NQ01	NAD(P)H Quinone oxidoreductase 1
OD	once daily
OTC	over-the-counter
PD	Parkinson’s disease
PDQ-39	39-Item Parkinson’s Disease Questionnaire
PO	by mouth
PT	Prothrombin Time
PTT	Partial Prothrombin 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
SAD	single ascending (oral) dose
SAE	serious adverse event
SD	standard deviation
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
UV	ultraviolet

XIII. SIGNATURE OF SPONSOR

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: 0 J /\JV CJ 1 \Signature: [redacted]

[redacted]

Edison Phaimaceuticals, Inc.
350 North Bernardo Ave
Mountain View, CA 94043

XIV. REFERENCES

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Summary of Changes

Amendment 2.0

EPI589-15-002

A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects

Protocol Number	EPI589-15-002
Original Protocol Date	27 April 2015
Amendment 1.0 Date	09 September 2015
Amendment 2.0 Date	04 January 2016
Study Sponsor	Edison Pharmaceuticals, Inc. 350 North Bernardo Avenue Mountain View, CA 94043
Sponsor's Representative	[redacted] Edison Pharmaceuticals, Inc. 350 North Bernardo Avenue Mountain View, CA 94043

1. KEY CHANGES TO THE PROTOCOL

Amendment 2.0 provides the following changes and their rationales:

Change	Rationale
Numerically indicated the ± day range of study drug administration	To clarify study drug administration duration
Additional detail for adaptive design rationale	To provide additional details on the purpose of and criteria for adaptive design component of protocol
Added examples of contraception	To provide more specific guidelines for methods of contraception
Added a post-treatment follow-up visit	To specify post-treatment follow-up and its time window to allow for assessment for events following discontinuation of study drug
Added details of study withdrawal criteria	To provide specific details for subject withdrawal from the study
Added warning about possible drug-associated phototoxicity since no data are yet available	To provide a warning of a potential side effect which has yet to be fully evaluated in preclinical studies

2. DESCRIPTION OF CHANGES TO THE PROTOCOL

Changes to the protocol by section appear in the table below. Administrative and editorial clarifications, corrections or adjustments may not be individually identified.

In this summary document, ***bold italic*** font indicates additions to existing text, and ~~strikethrough~~ font indicates deleted text. The actual amended protocol does not include bold or strikethrough font to indicate changes.

Protocol Section	Modification
Synopsis	Study design Open-label study with 30-day run-in phase and adaptive design component to include more subjects if deemed appropriate by investigators.
Synopsis	Planned number of subjects Approximately 40 subjects (20 with genetically-defined subtypes of PD and 20 drug-naïve idiopathic PD subjects). (Adaptive design component allows enrollment of up to 20 additional subjects with idiopathic PD to try to achieve a total of 20 subjects that have a biomarker response to EPI-589.)
Synopsis	Study duration 3 months ***(85 days ± 3 days)*** of study treatment preceded by a 1-month baseline parameter run-in period.
Synopsis; Section IV.D1	Inclusion criteria 3. ***Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., hormonal methods, including oral,***

<table>
<tr><td></td><td>subcutaneous and intrauterine; barrier methods, including [redacted] condom, [redacted] condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study treatment.<s>Agreement to use contraception if within reproductive years</s></td></tr>
<tr><td>Synopsis</td><td>Treatment
EPI-589 will then be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues. Post-treatment follow-up will be at least 10 days and up to 30 days after last dose.
<s>Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects.</s></td></tr>
<tr><td>I. Schedule of Assessments and Dosing Schedule</td><td>
<table>
<tr><td></td><td>Month 3
End of <s>Study</s>Treatment Visit</td><td>Post-Treatment Follow-up</td></tr>
<tr><td></td><td>Day 85
(± 3 days)</td><td>Up to 30 Days after Last Dose[e]</td></tr>
<tr><td>AE/SAE assessment[d]</td><td></td><td>✔[e]</td></tr>
<tr><td>Concomitant medications assessment</td><td></td><td>✔[e]</td></tr>
<tr><td>Post-Treatment Assessments[e]</td><td></td><td>✔[e]</td></tr>
<tr><td colspan="3">[e] AE/SAE and concomitant medication assessments conducted by telephone at least 10 days after last dose. Additional assessments to be determined at Investigator discretion.</td></tr>
<tr><td>Dosing Schedule</td><td>Month 3</td><td>Post-Treatment</td></tr>
</table>
</td></tr>
<tr><td>IV.A</td><td>EPI-589 will then be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues.

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects. Given that the investigational drug targets an enzyme key to glutathione synthesis and that glutathione depletion has been found to be associated with PD, we are seeking to determine the safety and potential biochemical benefit of EPI-589 in PD subjects as assessed by glutathione cycle biomarkers. If we determine that there are a subset of subjects with normal levels of glutathione who do not demonstrate biochemical changes following drug administration, and a subset of subjects with low levels of reduced glutathione who do respond to drug treatment, we would seek to enroll additional idiopathic PD subjects with low glutathione levels to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the study outcome metrics. EPI-589 will be administered for up to 3 months (85 days ± 3 days) unless discontinued for safety or tolerability issues.</td></tr>
<tr><td>IV.A5</td><td><u>A5. End of <s>Study</s></u><u>Treatment</u>

End of <s>study</s> treatment data will be collected at the last study visit Day 85 (± 3 days). AEs reported as ongoing at Day 85 (± 3 days), and/or any concomitant medications associated with such events 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.</td></tr>
<tr><td>IV.A6</td><td><u>A6. Post-Treatment Follow-up</u>

Post-Treatment Follow-up will be at least 10 days and up to 30 days after last dose: AE/SAE and concomitant medication assessments conducted by telephone. Additional assessments to be determined at Investigator discretion.</td></tr>
</table>

IV.C1	EPI-589 will then be administered for 3 months ***(85 days ± 3 days)*** unless discontinued for safety or tolerability issues. ***A post-treatment follow-up will be conducted up to 30 days after last dose.***
IV.C2	Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects ***to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the same study protocol and outcome metrics.***
V.B	End of ~~Study~~***treatment*** assessments will be conducted at the Month 3 study visit. Pharmacokinetic sampling takes place at Month 1 and Month 3.
V.C	**C.** End of ~~Study~~***Treatment*** Visit End of ~~Study~~ ***treatment*** visit takes place at Month 3 (Day 85 ± 3 days) and includes the assessments listed in Section VB2 Study Visit Assessments.
V.D	***D. Post-Treatment Follow-up*** ***Post-Treatment Follow-up will be at least 10 days and up to 30 days after last dose, with AE/SAE and concomitant medication assessments conducted by telephone. Additional assessments to be determined at Investigator discretion.***
V.H	H. Subject Withdrawals Subjects receive study treatment until treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice~~. Subjects may be withdrawn from the study at any time for reasons including the following~~***The following conditions require subject discontinuation from all study treatment:*** 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~~ ***a subject experiences a serious or severe adverse event that is deemed related to treatment with EPI-589 and in the Investigator's or the Sponsor's medical judgment continuation of treatment would be detrimental to the subject*** ~~***2.*** *At the specific request of the Sponsor (or designee)***~~ ~~***3.***~~ ***At the specific request of a regulatory agency for termination of treatment of an individual subject or all subjects under the protocol*** ~~***4.***~~ ***Subject participation in another clinical study using an investigational agent or investigational medical device*** ~~***5.***~~ ***Use of prohibited medications such as vitamins E and C beyond the recommended daily allowance; nortriptyline or fluvoxamine; and, for idiopathic subjects, MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease*** ~~***6.***~~ ***Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use medically accepted methods of contraception***

	7. ***If a subject becomes pregnant.*** 8. Significant noncompliance with the protocol ***in the opinion of the Investigator or the Sponsor***~~Additional protocol specific reasons~~
VII.D	Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker**-**responsive idiopathic PD subjects ***to achieve a higher number of subjects in whom we could understand the biochemical effects of the investigative drug and its potential clinical impact as assessed by the same study protocol and outcome metrics***.
IX.B1	These include, but are not limited to worsening neuromuscular function, depression, decline in cognitive function, loss of vision and other ophthalmological symptoms, loss of coordination and loss of speech. ***As there are no data available regarding EPI-589 phototoxicity, investigators are to advise subjects to take measures to minimize exposure to ultraviolet (UV) light for the duration of the study and for one week after the last dose.*** Edison Pharmaceuticals may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations.
IX.C2	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 ***of the pregnancy, fetus, and child*** will ~~be~~ ***continue*** ~~no longer than 6 to~~***for at least*** 8 weeks ~~following the estimated~~ delivery ~~date~~. While pregnancy itself is not considered an AE or SAE, all pregnancies should be reported using the same process as for SAEs.
XII	***UV ultraviolet***

End of Document

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EPI589-15-002
A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects

Original Protocol:	27 April 2015
Protocol Amendment 1.0:	09 September 2015

Edison Pharmaceuticals, Inc.
350 North Bernardo Avenue
Mountain View, CA 94043

Table of Contents

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PROTOCOL SYNOPSIS

Title of study	A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects
Protocol number	EPI589-15-002
IND number	126,795
EudraCT number	2015-001786-10
Original Protocol Date	27 April 2015
Protocol Amendment 1.0 Date	09 September 2015
Investigative Drug	EPI-589
Study Sponsor	Edison Pharmaceuticals Inc. 350 North Bernardo Avenue Mountain View, CA 94043
Investigators and Investigative Sites	• [redacted] USA • [redacted] UK
Study population	Approximately 40 subjects with Parkinson's disease (PD) including 20 subjects with genetically-defined subtypes
Rationale for Study	<u>Mitochondrial pathophysiology</u> It is now well appreciated that defects in mitochondrial function contribute to the pathophysiology of PD both in subjects with defined genetic defects as well as those with idiopathic forms of the disease. <u>High morbidity</u> Despite the available therapies for symptomatic relief, PD remains a highly morbid disease. There are no approved treatments for PD capable of modifying disease progression. <u>Pre-clinical efficacy data</u> EPI-589 is a redox active molecule that has demonstrated potency (EC50 < 100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with idiopathic and familial PD subtypes

	including PINK1, parkin and LRRK2.
Study objectives	Primary Objective To evaluate the effects of EPI-589 on safety as assessed by occurrence of drug-related serious adverse events in subjects with PD. Secondary Objectives To evaluate the effects of EPI-589 in subjects with PD on: 1. Glutathione cycle biomarkers as measured in blood, cerebral spinal fluid, and urine 2. Clinical disease state as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) 3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D 4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA) and 5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery and Asberg Depression rating scale (MADRS) 6. Pharmacokinetics 7. Hematology, blood chemistry, electrocardiogram
Study design	Open-label study with 30-day run-in phase and adaptive design component to include more subjects if deemed appropriate by investigators.
Planned number of subjects	Approximately 40 subjects (20 with genetically-defined subtypes of PD and 20 drug-naïve idiopathic PD subjects).
Study duration	3 months of study treatment preceded by a 1-month baseline parameter run-in period.
Test product, mode of administration, and dose	Test product EPI-589 in a tablet formulation at a strength of 250 mg Mode of Administration Oral with meal Dose EPI-589 500-mg BID
Reference therapy, dose, and mode of	None

administration

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. Hoehn and Yahr stage ≤ 2.5
2. Ambulatory with or without assistance
3. Agreement to use contraception if within reproductive years
4. Willingness and ability to comply with study procedures
5. Stable regimen of dietary supplements for 30 days prior to enrollment
6. Abstention from use of other investigative or non-approved drugs for the duration of the trial

For Idiopathic Subjects

7. *For idiopathic subjects*: a diagnosis of early idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit
8. *For idiopathic subjects*: must not yet require symptomatic medications for PD and not expected to require such treatment before the end of the study
9. For idiopathic subjects: age 40 to 75 years
10. *For idiopathic subjects*: within 5 years of diagnosis of Parkinson's disease

For Genetic Subtype Subjects

11. *For genetic subtype subjects*: a confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LARK2 or other mitochondrial genetic subtype
12. *For genetic subtype subjects*: age 21 to 75 years

13. *For genetic subtype subjects*: stable medication regimen of PD drugs for 30 days (except 60 days for rasagiline) prior to enrollment

Exclusion criteria

1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation
2. Use of antioxidant supplements, specifically vitamins E and C beyond the recommended daily allowance
3. Other Parkinsonian disorders
4. MoCA score of <24
5. Revised Hamilton Rating Scale for Depression ≥ 11
6. Parkinsonism due to drugs or toxins
7. Diagnosis of any other clinically significant neurologic disease that will confound the assessment of effect of study drug on disease progression
8. Malignancy within past two years
9. Pregnant or plans to become pregnant or breast feeding
10. History of stroke
11. History of brain surgery
12. Hepatic insufficiency with liver function tests (LFTs) > 3 times upper limit of normal
13. Renal insufficiency as defined by creatinine > 1.5 times normal
14. End stage cardiac failure
15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD

For Idiopathic Subjects

16. *For idiopathic subjects*: use of any MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease for idiopathic subjects
17. *For idiopathic subjects*: use of nortriptyline or fluvoxamine 60 days prior to enrollment

Treatment

Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months unless discontinued for safety or tolerability issues. Under an adaptive

	design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects.
Efficacy variables	1. Blood-based glutathione biomarkers 2. CNS biomarkers 3. Urine-based biomarkers 4. MDS-UPDRS 5. Non-motor Symptoms Scale (NMSS) 6. PDQ-39 7. EQ-5D 8. MoCA 9. Beck Depression Inventory (BDI) 10. Montgomery & Asberg Depression rating scale (MADRS) 11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy) 12. Pharmacokinetics
Safety variables	Clinical 1. Routine assessments of AEs and SAEs 2. Dose limiting toxicities 3. Electrocardiogram 4. C-SSRS 5. Laboratory 6. Routine serum chemistries with liver function tests 7. Routine hematology tests with coagulation tests
Statistical Considerations	<u>Data Analysis</u> This is a within-subject, controlled open-label study seeking to determine the safety and tolerability of EPI-589 in patients with PD as well as to determine if EPI-589 can alter the biochemical signature of PD as assessed by peripheral blood biomarkers, CNS biomarkers, brain imaging biomarkers, and urine biomarker analysis. In addition, data on a number of disease-relevant clinical measures will be collected.

I. SCHEDULE OF ASSESSMENTS AND DOSING SCHEDULE

Tests	-2 to -1 Months		Day 0	Month 1	Month 2	Month 3 End of Study
	Screening	Run-in (± 30 days)	Baseline	Day 29 (± 3 days)	Day 57[d] (± 3 days)	Day 85 (± 3 days)
Informed consent	✓					
Inclusion/Exclusion criteria	✓					
Past Medical history	✓					
Previous genetic testing review	✓					
Physical exam & Vital signs	✓		✓	✓		✓
Height & weight	✓		✓[a]	✓		✓
12-lead ECG	✓		✓[a]	✓		✓
Hematology (including coagulation panel)	✓		✓[a]	✓		✓
Serum Chemistry	✓		✓[a]	✓		✓
Pregnancy test[b]	✓		✓	✓		✓
C-SSRS			✓	✓		✓
Montreal Cognitive Assessment	✓					✓
DaTscan	✓					
Revised Hamilton Rating Scale for Depression	✓					
Subject enrolls in study		X				
Blood-based glutathione cycle biomarkers		✓	✓	✓		✓
Lumbar puncture (CNS biomarkers)		✓				✓
Urine-based biomarkers		✓	✓	✓		✓
MDS-UPDRS		✓	✓	✓		✓
Timed motor tests (for subjects on dopamine therapy)		✓	✓			✓
NMSS, PDQ-39, EQ-5D			✓			✓
BDI, MADRS			✓			✓
Drug plasma concentration[c]				✓[c]		✓[c]
AE/SAE assessment[d]				✓	✓[d]	✓[d]
Concomitant medications assessment	✓	✓	✓	✓	✓[d]	✓[d]

a. Screening values can be used if done within one month of baseline.
b. Female subjects of childbearing potential must have a negative pregnancy test.
c. Full plasma concentration profile will be obtained at Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing from the first 10 subjects to complete 1 month of therapy at each site.
d. Month 2 assessments can be done by telephone. Any new AEs and associated concomitant medications reported at Month 3 must be followed for 30 days; this follow up may be conducted by telephone.

Dosing Schedule				Month 1	Month 2	Month 3
EPI-589 500-mg BID				✓	✓	✓

II. INTRODUCTION

A. Background Information and Rationale

Parkinson's disease (PD) is a highly morbid neurodegenerative movement disorder that has a number of neuromuscular, cognitive and neuropsychiatric manifestations as well as non-neurological symptoms. PD is the second most common neurodegenerative disorder with an estimated prevalence of 6.3 million people worldwide (EPDA).

PD has long been considered a non-genetic (idiopathic) disease; however, about 5% of patients have an identifiable mutation. Disease onset typically occurs after age 50, however, in a subset of patients, disease onset can occur at a younger age. The primary motor symptoms result from death of dopamine-producing cells in the pars compacta region of the substantia nigra. However, the mechanisms underlying this cell death and disease pathology remain poorly understood. There is no approved treatment for PD capable of modifying disease progression. Current therapies partially address disease motor symptoms through levodopa or dopamine agonists or other agents, and other disease symptoms (e.g. neuropsychiatric symptoms), but disability tends to increase over time despite these treatments.

The association of PD with mitochondrial pathology and high levels of oxidative stress are well established. Increased levels of oxidative stress have been consistently measured in post-mortem specimens from PD patients (Maarouf 2012, Reale 2012). The occurrence of PD-like symptoms in heroin addicts exposed to MPTP in the 1980s established a first link between PD and mitochondrial injury (Langston 1983, Dauer and Przedborski 2003). MPTP inhibits complex 1 of the mitochondrial respiratory chain and induces degeneration of dopaminergic cells through oxidative stress-mediated injury. The link between mitochondrial injury and PD was further strengthened by the induction of PD symptoms following exposure to another neurotoxic complex 1 inhibitor, rotenone (Betarbet et al 2000, Greenamyre et al. 2003), which like MPTP has come to be used in pre-clinical testing for its phenotypic similarities to PD.

Furthermore, the identification of genetic mutations such as PINK1, parkin, LRRK2 and others in mitochondrial genes in familial PD patients provided the strongest link between the mitochondria and PD (Winklhofer and Haass 2010). Normally these genes influence oxidative balance and provide neural protection of the dopaminergic neurons that are affected by PD. PINK1 and parkin are involved in protecting against oxidative stress (OS) and overabundant reactive oxygen species (ROS), and are implicated in cell morphology and dynamics, as well as in the preferential degradation of dysfunctional mitochondria or "mitophagy" (Ashrafi et al. 2014). Mutant LRRK2 leads to the accumulation of misfolding intracellular protein accumulations, cell stress and apoptosis (Giasson et al. 2006, Zhu et al. 2006).

The importance of oxidative stress in PD pathology is further substantiated by the measurement of decreased levels of reduced glutathione in the brains of patients with PD (Holmay et al. 2013). Glutathione levels are low at very early stages of PD and correlate with disease severity (Riederer et al. 1989), and experimental induction of glutathione depletion leads to mitochondrial complex I dysfunction (Jha et al, 2000;). Reduced glutathione is an essential intermediary

metabolite that serves as the primary native cellular antioxidant. In a state of high oxidative stress, elevated levels of ROS outstrip the supply of glutathione (GSH) resulting in depletion of GSH and ROS-mediated cell death.

Given the important role of oxidative stress and mitochondrial pathology in PD, a redox-active therapy that could target key pathways in cellular OS response pathways may hold promise for the treatment of PD.

B. Rationale for the Study of EPI-589 in Parkinson's Disease

EPI-589 is a redox active molecule that has demonstrated potency (EC50 <100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with idiopathic and familial PD genetic subtypes including PINK1, parkin and LRRK2.

In these cell-based assays, primary fibroblasts from patients (and control) were pre-incubated with and without test compound, then treated with L-buthionine-(S,R)-sulfoximine (BSO), a GSH synthesis inhibitor, to initiate depletion of cellular GSH. GSH depletion has been shown to lead to OS and disruption of calcium homeostasis resulting in loss of the mitochondrial membrane potential and cell death. Under these conditions, the control cells are resistant to the stress and the fibroblast cells from patients with disease indications die within 36 to 48 hours. Pretreatment of cells with EPI-589 prior to initiation of GSH depletion potently protected against oxidative stress-mediated cell death, with EC_{50} response concentrations of 16 to 52 nM. (Table 1).

Table 1: Cell Line Rescue with EPI-589 in Parkinson's Disease Genetic Subtypes

	EPI-589 **EC_{50} (nM range)**
PINK1	26-36
LRRK2	16-18
parkin	42-52

C. Name and Description of Investigational Product

The IUPAC name of 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 derived from resolved (R)-Trolox®, a derivative of vitamin E in the form of a pale yellow to yellow solid. The EPI-589 drug product will be provided in a 250-mg tablet formulation.

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. In 28-day and 91-day repeat-dose toxicity studies in rat and cynomolgus monkey, the no observed adverse effect level (NOAEL) was 300 mg/kg/day, corresponding to combined mean Cmax values of 37,717 to 56,500 ng/mL (rat) and 14,300 to 16,417 ng/mL (monkey), and a combined mean area under the plasma concentration-time curve from time zero to the last measurable concentration (AUClast) value of 149,495 to 297,000 ng.h/mL (rat) and 47,300 to 67,656 ng.h/mL (monkey) (Studies 1660-038, 1660-039, 1660-063, and 1660-064).

A phase 1 clinical study demonstrated that healthy subjects administered 500 mg EPI-589 BID for 14 days showed a mean Cmax value of 1,890 ng/mL and a mean AUClast value of 5,240 ng.h/mL (Study EPI589-14-01). These plasma concentrations are well below the mean exposure values in monkey associated with the NOAEL in the toxicity studies, corresponding to safety margins of approximately 7- to 8-fold for the mean Cmax and 9- to 12-fold for the mean AUC.

During the 28-day repeat-dose toxicity studies, rat and monkey were exposed to up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-039 and 1660-038). The NOAEL for both studies was 300 mg/kg/day. Rats exposed to 1,000 mg/kg/day exhibited adverse 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 showing corresponding microscopic pathology. The majority of these findings were resolved following the 28-day recovery period. Monkeys exposed to 1,000 mg/kg/day showed significant test-article related morbundity that resulted in half the animals in the high dose group being euthanized on Days 3 and 4 and the remaining animals being euthanized on Day 9. These animals exhibited significant elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values, and microscopic findings in the kidney, liver, skeletal muscle, heart, and lymphoid tissues. In several of the animals the primary cause of morbidity was determined to be test-article related renal tubular degeneration/necrosis.

During the 91-day repeat-dose toxicity studies, rat and monkey were exposed to up to 300 mg/kg/day EPI-589 PO (Studies 1660-063 and 1660-064). The NOAEL for the rat study was 300 mg/kg/day and the no observed effect level (NOEL) for the monkey study was 300 mg/kg/day. [redacted] rats exposed to 300 mg/kg/day and [redacted] rats exposed to ≥ 100 mg/kg/day exhibited mild test-article related effects on hematology parameters consistent with hemolysis and bone marrow regeneration. These findings were not considered adverse.

Development and reproductive toxicology studies were conducted in rat and rabbit at doses up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-069, 1660-067, and 1660-068). The NOAEL for reproductive toxicity in rat was demonstrated to be 1,000 mg/kg/day (1660-069). The NOAEL

for developmental toxicity in rat and rabbit during the embryofetal studies was deemed to be 300 mg/kg/day (Studies 1660-067 and 1660-068). Rats exposed to 1,000 mg/kg/day exhibited 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. Rabbits exposed to 1,000 mg/kg/day exhibited 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 (Study EPI589-14-01) and rabbits exposed to 1,000 and 300 mg/kg/day EPI-589 is approximately 179- to 236-fold and 47- to 50-fold, respectively. 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 (Study AD58AS.502ICH.BTL); 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 (Study AD58AS.331ICH.BTL); and negative in the in vivo micronucleus assay in rat (Study AD58AS.125012ICH.BTL). These data indicate a low clinical mutagenicity risk.

Primary pharmacodynamics studies demonstrated that EPI-589 is a potent rescue agent in cellular models of diseases of energy metabolism and oxidative stress. In vitro cellular models utilizing primary human fibroblasts from patients with ALS, Parkinson's disease and other diseases characterized by high levels of oxidative stress, or striatal cells derived from mouse models of Huntingdon's disease were used to assess the potential of EPI-589 to mitigate the harmful effects of oxidative stress (Studies EPI-BA-000216, EPI-BA-000363, and EPI-BA-000362). Pretreatment of patient cells with EPI-589 potently protected against oxidative stress-mediated cell death in a concentration dependent manner. Furthermore, EPI-589 normalized 3-nitrosotyrosine (3NT) levels, a biomarker of oxidative stress, and increased glutathione levels in mouse striatal cells under oxidative stress conditions.

In secondary pharmacodynamics in vitro receptor/ion channel binding studies, EPI-589 did not significantly affect off-target molecular targets (Study EPI-BA-159). In safety pharmacology studies, EPI-589 did not significantly affect ion channel current in the hERG assay (Study 130719.FEK); did not affect ECG parameters during the 28-day and 3-month repeat-dose toxicology studies in monkey at doses up to 1,000 mg/kg/day (only Day 1 data collected for animals administered 1,000 mg/kg/day and up to Day 91 data collected for animals administered up to 300 mg/kg/day) (Studies 1660-038 and 1660-064); and did not change respiratory function or adversely impact neurobehavioral function in rat at doses up to 1,000 mg/kg (Studies 1660-051, 1660-050, and 1660-063).

In single dose exposure PK studies, EPI-589 was absorbed rapidly in rat, dog, and monkey, with mean T_{max} values ranging from .08 to 1 hour and mean T1/2 values ranging from 3.7 to 5.0 hours (Studies EPI-BA-53, EPI-BA-59, EPI-BA-72, and EPI-BA-302). EPI-589 does not significantly induce cytochrome P450 (CYP) enzymes and appears to be metabolized by reductases in the

liver cytosol and microsomal subcellular fractions and to a lesser extent by the family of CYP enzymes (Studies MC12M-0037 and MC14M-0018).

EPI-589 exhibited weak direct inhibition of CYP2B6, CYP2C8, CYP2C9, and CYP3A4/5 (both midazolam and testosterone as probe substrates) with estimated IC_{50} (μM) values and R values based on free plasma concentrations (shown in parentheses) of 28 (1.25), 40 (1.18), 92 (1.08), 34 (1.21), and 53 (1.13), respectively (Study MC14M-0020)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.

D2. Clinical Studies

Phase I Study EPI589-13-022 evaluated the pharmacokinetics, safety and tolerability of single ascending oral doses (SADs) of EPI-589 in healthy subjects and a preliminary evaluation of safety and tolerability data was performed. Sixteen AEs were reported in the 36 subjects who received administration of EPI-589. Ten subjects (27.8%) who received EPI-589 (and 2 subjects, 20% on placebo) reported AEs that were assessed as related. All were mild and resolved during the study, with the exception of a common cold (1 subject) and cold sore (1 subject). 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. Twenty-six subjects (65.0%) on EPI-589, and 8 subjects (80%) on placebo reported AEs. Twenty-four of 34 AEs were considered by the Investigator to be related to EPI-589. Nineteen subjects (47.5%) on EPI-589, and 6 subjects (60%) on placebo reported AEs that were assessed as related. All adverse events were mild, except for 1 AE which was moderate (unrelated brain contusion). All AEs were resolved during the study, with the exception of one, which was a common cold. 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 the MAD study it may be concluded that there is no objection to proceed with treatment with 250-mg, or 500-mg doses of EPI-589.

E. Human Pharmacokinetics

EPI-589 was fast absorbed following oral administration in SAD Study EPI589-13-022. The median C_{max} was attained approximately within 1 hour under fasted conditions after dosing. The median T_{max} values were attained in 0.50 to 1.00 hours over the dose range of 50 to 1000 mg under fasted conditions and 3.01 hours at the 500 mg dose level under fed conditions. Mean half-life ranged from 5.55 to 10.7 hours over the dose range of 50 to 1000 mg under fasted conditions and 4.91 hours at the 500 mg dose level under fed conditions. Half-life was independent of the dose levels over the dose range of 50 to 1000 mg under fasted conditions. The rate of EPI-589 absorption, as measured by C_{max}, was decreased by 24.07% under fed conditions at the 500 mg

dose level. The extent of absorption as measured by AUCs (AUC_{0-t} or AUC_{0-inf}) was not affected under fed conditions in the 500 mg dose groups.

In MAD study EPI589-14-01, 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 of various ages and smoking status. No significant effects of age or smoking on EPI-589 pharmacokinetics were observed in this study. Dose proportionality existed in the exposures (AUC_{0-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

EPI589-15-002: A Phase 2A Safety and Biomarker Study of EPI-589 in in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects.

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 meals.

H. Compliance Statement

This study will be conducted in full accordance with all applicable research policies and procedures, the EU Clinical Trials Directive, all applicable EU and 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, will obtain consent and will 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.

I. Relevant Literature and Data

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

III. STUDY OBJECTIVES

A. Primary Objective

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 PD.

B. Secondary Objectives

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

1. Glutathione cycle biomarkers as measured in blood, cerebral spinal fluid, and urine
2. Clinical disease state as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D
4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA)
5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery & Asberg Depression rating scale (MADRS)
6. Pharmacokinetics
7. Hematology, blood chemistry, electrocardiogram

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IV. INVESTIGATIONAL PLAN

A. General Schema of Study Design

Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months unless discontinued for safety or tolerability issues.

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects.

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 run-in scans, CNS, blood-based biomarker, urine-based biomarker and clinical measurements will be collected.

A3. Baseline

Baseline assessments, scans, blood-based biomarker, urine biomarker, 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-based biomarker, urine biomarker, and clinical measurements will be collected at Day 29 (± 3 days) and Day 85 (± 3 days).

A5. End of Study

End of study data will be collected at the last study visit Day 85 (± 3 days).

AEs reported as ongoing at Day 85, any associated concomitant medications associated with such events, and any events occurring within 30 days of last dose will be followed for 30 days.

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 biomarker and clinical baseline measurements. EPI-589 will then be administered for 3 months unless discontinued for safety or tolerability issues.

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

This study will be conducted at two study sites:

- [redacted] UK
- [redacted] USA.

Approximately 40 subjects with PD are projected:

- 20 with genetically-defined subtypes
- 20 PD drug-naïve

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects.

D. Study Population

D1. Inclusion Criteria

1. Hoehn and Yahr stage ≤ 2.5
2. Ambulatory with or without assistance
3. Agreement to use contraception if within reproductive years
4. Willingness and ability to comply with study procedures
5. Stable regimen of dietary supplements for 30 days prior to enrollment
6. Abstention from use of other investigative or non-approved drugs for the duration of the trial

For Idiopathic Subjects

7. *For idiopathic subjects*: a diagnosis of early idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit
8. *For idiopathic subjects*: must not yet require symptomatic medications for PD and not expected to require such treatment before the end of the study
9. *For idiopathic subjects*: age 40 to 75 years
10. *For idiopathic subjects*: within 5 years of diagnosis of Parkinson's disease

For Genetic Subtype Subjects

11. *For genetic subtype subjects*: a confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LARK2 or other mitochondrial genetic subtype
12. *For genetic subtype subjects*: age 21 to 75 years
13. *For genetic subtype subjects*: stable medication regimen of PD drugs for 30 days (except 60 days for rasagiline) prior to enrollment

D2. Exclusion Criteria

1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation
2. Use of antioxidant supplements, specifically vitamins E and C beyond the recommended daily allowance
3. Other Parkinsonian disorders
4. MoCA score of <24
5. Revised Hamilton Rating Scale for Depression ≥ 11
6. Parkinsonism due to drugs or toxins
7. Diagnosis of any other clinically significant neurologic disease that will confound the assessment of effect of study drug on disease progression
8. Malignancy within past two years
9. Pregnant or plans to become pregnant or breast feeding
10. History of stroke
11. History of brain surgery
12. Hepatic insufficiency with liver function tests (LFTs) > 3 times upper limit of normal
13. Renal insufficiency as defined by creatinine > 1.5 times normal
14. End stage cardiac failure
15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD

For Idiopathic Subjects

16. *For idiopathic subjects*: use of any MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease for idiopathic subjects
17. *For idiopathic subjects*: use of nortriptyline or fluvoxamine 60 days prior to enrollment

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V. STUDY PROCEDURES

A. Screening Visit

Screening evaluations will be performed within two months of first dose. The Investigator will inform each prospective subject of the nature of the study, explain the potential risks, and must 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. Receipt and review of previous testing including genetic tests
4. Physical examination including vital signs
5. Height and weight
6. 12-lead ECG
7. Laboratory assessments for hematology, coagulation, and serum chemistry (See Sections VI.D3.a and VI.D3.b)
8. Urine pregnancy test (women of childbearing potential must have a negative urine pregnancy test; see Section VI.D3.c)
9. MoCA
10. DaTscan
11. Revised Hamilton Rating Scale for Depression
12. Concomitant medications assessment (last 60 days prior to enrollment)

A1. Run-in Assessments

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 within one month for Run-in assessments. These will 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. Blood-based glutathione cycle biomarkers
2. CNS biomarkers (lumbar puncture)
3. Urine biomarkers
4. MDS-UPDRS
5. Timed motor tests (for subjects on dopamine therapy)
6. Concomitant medications review

B. Treatment Phase

After the Run-in phase, the subject must return to the clinic within 30 days (± 3 days) for baseline assessments. In-clinic study visits are scheduled at Month 1 and Month 3. The Month 2 study assessments can be conducted via telephone. End of Study assessments will be conducted 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 including vital signs
2. Height and weight*
3. 12-Lead ECG*
4. Blood-based GSH cycle biomarkers
5. Urine-based biomarkers
6. Laboratory assessments for hematology, coagulation and serum chemistry*
7. Urine pregnancy test (females of child bearing potential)
8. C-SSRS (Columbia Suicide Severity Rating Scale)
9. MDS-UPDRS
10. NMSS, PDQ-39, EQ-5D
11. BDI, MADRS
12. Timed motor tests (for subjects on dopamine therapy)
13. Concomitant medications review

* Screening results for these assessments may be used if obtained within 1 month of Baseline.

B2. Study Visit Assessments

- Month 1 Clinic Visit (Day 29 ± 3 days):

The following will be assessed or performed at the Month 1 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry
5. Urine pregnancy test (females of child bearing potential)
6. C-SSRS
7. Blood-based GSH cycle biomarkers
8. Urine-based biomarkers
9. MDS-UPDRS
10. Pharmacokinetics: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.
11. AE assessments
12. Concomitant medications review

- Month 2 Visit (Day 57 ± 3 days)

Month 2 assessments can be conducted by telephone and must include review of:

1. Concomitant medication
2. AEs

- Month 3 Clinic Visit (Day 85 ± 3 days)

The following will be assessed or performed at the Month 3 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry
5. Urine pregnancy test (females of child bearing potential)
6. C-SSRS
7. Blood-based GSH cycle biomarkers
8. Urine-based biomarkers
9. CNS biomarkers
10. MDS-UPDRS
11. Pharmacokinetics: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.
12. AE assessments
13. Concomitant medications review
14. MoCA
15. NMSS, PDQ-39, EQ-5D
16. BDI, MADRS
17. Timed motor tests (for subjects on dopamine therapy)

B3. Pharmacokinetics

Plasma concentration samples will be collected from the first 10 subjects to complete 1 month of therapy at each site, at the following time points:

- Month 1 (Day 29 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose
- Month 3 (Day 85 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose

B4. Early Termination Study Visit

Subjects who terminate from the study after receiving first dose and prior to the completion of all scheduled visits should have the end of study visit assessments completed as soon as possible.

C. End of Study Visit

End of Study visit takes place at Month 3 (Day 85 ± 3 days) and includes the assessments listed in Section VB2 Study Visit Assessments.

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 study visit windows, assessments will be made at the Investigator's discretion. All study relevant unscheduled visit assessments will be recorded in the case report form (CRF) using the supplemental visit CRF pages.

E. Concomitant Medication

Any medication taken by a subject ≤ 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 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 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 and for the duration of the study in a trial of a device, drug or other therapy for PD
3. Use of MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease for idiopathic subjects
4. Use of nortriptyline or fluvoxamine

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. At the specific request of the Sponsor (or designee)
4. 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 IX.B.

Evaluations should 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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VI. 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 PD.

B. Secondary Endpoints (Efficacy)

1. Blood-based biomarkers
2. CNS-based biomarkers
3. Urine-based biomarkers
4. MDS-UPDRS
5. NMSS
6. PDQ-39
7. EQ-5D
8. MoCA
9. BDI
10. MADRS
11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)
12. Pharmacokinetics

C. Secondary Endpoints (Safety)

1. Routine assessments of AEs and SAEs
2. Dose limiting toxicities
3. Routine serum chemistries with liver function tests
4. C-SSRS
5. Routine hematology tests with coagulation tests
6. Electrocardiogram

D. Screening and Baseline Evaluation

D1. Physical Examination

Complete physical exams will be conducted (excluding genital/rectal exam) at protocol specified study visits. 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, heart, abdomen, and extremities.

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).

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

D2. Height and Weight

Weight (kg) will be measured in ordinary indoor clothing (i.e., street clothes, scrubs, etc.) with shoes off. Height will be recorded in centimeters (cm).

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.

D3. Laboratory Evaluations

Subjects 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 I).

a. 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 (WBC) 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) with INR, partial thromboplastin time (PTT), activated (aPTT)

b. Serum chemistry

1. Liver: Alkaline Phosphatase (ALP), ALT (serum glutamic-pyruvic transaminase [SGPT]), AST (serum glutamic-oxaloacetic transaminase [SGOT]), bilirubin (total and direct), gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH)
2. Renal: blood urea nitrogen (BUN), and creatinine
3. Electrolytes: sodium, potassium, chloride, and carbon dioxide (CO2) as bicarbonate
4. General: creatine phosphokinase (CPK), creatine kinase (CK), and troponin (at baseline only); total protein, 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

c. Urine pregnancy test

1. Human chorionic gonadotropin (HCG) beta subunit will be measured on all female subjects of childbearing potential.

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.

Diagnoses associated with any NIH Common Terminology Criteria for Adverse Events (CTC v4.03) Grade 3 or 4 laboratory abnormalities will be recorded as SAEs on the CRF. Repeated and verified ≥ Grade 3 laboratory tests will be reported as an SAE to the Sponsor and the IRB per institutional requirements. The recorded event 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.

D4. 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.

E. Sample Collection Procedures, Bioanalytical Methods and Sample Shipment

Subject samples will be identified by unique sample codes.

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

F. Efficacy Evaluations

F1. Glutathione Cycle Biomarkers

Blood, urine, and CNS levels of oxidized and reduced GSH as well as GSH metabolites will be used to evaluate EPI-589 target engagement and ability to correct a key biochemical aspect of disease pathology.

F2. Parkinson's Disease Rating (MDS-UPDRS)

The MDS-UPDRS is a tool for monitoring the impact of PD, the degree of disability caused, and complications from treatment. Part I evaluates nonmotor experiences of daily living; Part II evaluates motor experiences of daily living; Part III is a motor examination and includes the Hoehn and Yahr scale; Part IV examines motor complications (e.g., motor fluctuations and dyskinesias).

Several questions from Part I and all questions from Part II are designed to be amenable to a patient/caregiver questionnaire format; the remaining interview (Part I and Part III) and

examination (Part IV) are designed with the expectation they can be completed within 30 minutes. Each item is measured on a five-point scale.

F3. Non-motor Symptoms (NMSS)

Non-motor symptoms are evaluated using the NMSS which is divided into 30 questions in 9 different domains including such symptoms as dribbling saliva, constipation, depression, sleep disorders, apathy, hallucinations and dementia. Symptoms are quantified based on their severity (using a scale of 0 to 3) and frequency (using a scale of 0 to 4). The final cumulative scores are derived from adding up the product of the frequency score times severity score for each of the 30 questions.

F4. Parkinson's Disease Questionnaire (PDQ-39)

PDQ-39 is a self-administered questionnaire for patients with PD that has 39 questions relating to eight key areas of health and daily activities, including both motor and non-motor symptoms. It is scored on a scale of 0 to 100, with lower scores indicating better health, and high scores more severe symptoms.

F5. EQ-5D

EQ-5D is a questionnaire designed to provide measures of health-related quality of life states, consisting in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

F6. Montreal Cognitive Assessment (MoCA)

MoCA is a 30-point questionnaire for cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Severity ranges are approximately: 26 to 30 normal; 18 to 26 mild cognitive impairment; 10-17 moderate cognitive impairment; < 10 severe cognitive impairment.

F7. Beck Depression Inventory (BDI)

The BDI is a self-reporting inventory that measures characteristic attitudes and symptoms of depression, including physical symptoms. Twenty-one questions have four responses each (rated 0 to 3) with a total cumulative score scale ranging from 1-10 considered normal) > 40 (extreme depression).

F8. Montgomery and Asberg Depression rating scale (MADRS)

The MADRS is a clinician-rated tool for measuring changes in depressive symptom severity. Ten core symptoms and cognitive features are rated on a severity scale of 0 to 6. Higher scores indicate increasing depressive symptoms.

F9. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)

Timed motor tests are simple, objective, quantitative measures for the assessment of Parkinson's disease. They include, in an on-medication and an off-medication state, timed recorded physical movements.

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VII. 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.

A1. Analysis Populations

Demographic characteristics and baseline efficacy data will be presented and summarized by treatment group for all subjects in the efficacy intent to treat (EITT) population. Demographic information will also be summarized by treatment group 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. CNS biomarkers
3. Urine-based biomarkers
4. MDS-UPDRS
5. NMSS
6. PDQ-39
7. EQ-5D
8. MoCA
9. BDI
10. MADRS
11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)
12. Pharmacokinetics

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 PD.

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 40 subjects (20 with genetically-defined subtypes of PD and 20 PD drug-naïve subjects). Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects.

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VIII. STUDY MEDICATION

A. Description

EPI-589 is presented as an immediate release film-coated tablet. Each tablet contains 250 mg of EPI-589 and the following compendial excipients: lactose, 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, in compliance 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 HPDE 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]).

C. 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 verification with subject-completed diary cards and returned used drug supply.

D. Drug Accountability

Dosing information will be captured on a subject Dosing Diary Form. This form is part of the 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 Investigator study file to assure the study medication is 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 either be 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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IX. 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 in accordance with the IRB policies and as detailed below. AEs that are not serious will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

B1. Safety Guidance

Based on the known clinical manifestations of Parkinson's disease, we expect that many AEs could occur during the course of the trial that are well documented to occur as the results of the natural history of this disease. These include, but are not limited to worsening neuromuscular function, depression, decline in cognitive function, loss of vision and other ophthalmological symptoms, loss of coordination and loss of speech.

Edison Pharmaceuticals 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, Edison Pharmaceuticals should be provided with a copy of any post-mortem findings, including histopathology.

C. Definition of an Adverse Event

C1. Adverse Event

An 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” or “AE”.

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)

An 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; or
5. A congenital anomaly/birth defect.

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 subject 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 an SAE which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether other AEs, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject, require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

[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, all pregnancies should be reported using the same process as for SAEs. Any pregnancy complications or an outcome other than a healthy, normal outcome will be recorded as an AE or SAE.

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.

C3. Non-serious Adverse Event

A non-serious AE 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 and reappears with re-introduction 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 indicated.

Grade 2 – Moderate limitation in activity, some assistance may be needed; minimal noninvasive medical intervention/therapy indicated.

Grade 3 – Severe limitation in activity, assistance usually required; medical intervention/therapy required; hospitalization or prolongation of hospitalization indicated; disabling.

Grade 4 – Extreme limitation in activity, significant assistance required; urgent medical intervention/therapy required; life-threatening consequences.

Grade 5 – Death

C6. Definition of Unexpected Adverse Event

Any AE, the specificity or severity of which is not consistent with those listed in the current investigator's brochure is considered "unexpected."

C7. Notification of SAEs

The Investigator is responsible for promptly notifying the IRB/IEC of all study on-site SAEs 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 MedWatch or CIOMs form (as appropriate).

SAEs (whether unexpected or expected AEs) must be documented on the designated SAE form. The SAE must be reported to the medical expert and appropriate Edison or Edison-assigned pharmacovigilance staff within 24 hours, according to regulatory, Sponsor, or ICH-E6 Good Clinical Practice, followed by the SAE form within two 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 Investigator and/or Medical Expert must also inform the Study Monitor and the Sponsor in all cases. Any SAEs must also be reported to the IRB/IEC. The Sponsor or designee will ensure that all legal reporting requirements are met.

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 a follow-up SAE forms.

The instructions to sites for the completion of SAE reports give detailed guidance on the reporting of SAEs and AEs initially reported as non-serious that become serious. When a non-serious event becomes serious, details must be forwarded immediately to the Medical expert and Edison or Edison-assigned 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 reported to the relevant competent authorities.

In the US, all fatal or life-threatening suspected unexpected serious adverse events assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA as soon as possible (i.e., by telephone or facsimile transmission), but no later than 7 calendar days after first knowledge by the Sponsor that a report qualifies as a suspected unexpected fatal or life-threatening reaction. All unexpected serious adverse events, other than fatal or life-threatening, assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA within 15 calendar days from the day the Sponsor determines that the information qualifies as a SUSAR.

In the UK, the Sponsor or trial investigator must act immediately or at least within 24 hours after becoming aware of a SUSAR by informing the MHRA's Clinical Trial Unit by telephone. The MHRA must then be informed in writing within 3 days of the incident. All SUSARs originating in the UK or originating outside the UK involving the same medicinal product are to be reported. Fatal or life-threatening SUSARs are to be reported as soon as possible, but no later than after 7 days. Any additional relevant information must be sent within 8 days of the report. Non-fatal or non-life-threatening SUSARs are to be reported as soon as possible but no later than 15 days after becoming aware of the reaction.

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. All SAEs should be followed until either resolved or stable.

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 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.

X. 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 Edison 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 Edison. 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 Edison 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 (0.001%), a systematic review of the database will be undertaken and corrections will be made to achieve an error rate of less than 0.001%.

AEs will be coded using MedDRA, version (14.3). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary, March 2014.

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 or 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, and the General Data Protection Regulation (GDPR).

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 EPI-589-14-01 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 PD. Therefore, we cannot assure that subjects will benefit from treatment with EPI-589. Potential benefits may manifest in a variety of ways, such as in disease-related parameters, functioning, and quality of life.

G3. Risk-Benefit Assessment

There are no effective and/or approved disease modifying treatments available for PD, 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 hold benefit for patients with PD. This is the first study to better understand EPI-589 target engagement and potential therapeutic

benefit in subjects with PD. 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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XI. PUBLICATION

A. Use of Study Results

All information concerning the product, as well as any matter concerning the operation of Edison (such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by Edison and are unpublished), are confidential and must remain the sole property of Edison. 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 Edison 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 Edison. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

This Study is part of a multicenter clinical research study. Accordingly, 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 while this Study is being conducted at other center/s. Only after the completion of this Study at all other centers, provision of the data to the FDA or EMA for review and comment, and publishing the combined data from all of the centers, may the Principal Investigator 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 Edison, Edison will allow the Investigator or CRO 60 days for full review of the manuscript before publication.

XII. LIST OF ABBREVIATIONS

AE	adverse event
AI	accumulation index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AR	accumulation ratio
BDI	Beck Depression Inventory
BID	twice daily
BSO	L-buthionine-(S,R)-sulfoximine
C-SSRS	Columbia-Suicide Severity Rating Scale
CBC	complete blood count
CFR	Code of Federal Regulations
CK	creatinine kinase
CNS	central nervous system
CoQ10	Coenzyme Q 10
CRF	Case Report Form
CRO	Contract Research Organization
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DaT	dopamine transporters
DSMB	data safety monitoring board
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EITT	efficacy intent-to-treat
EPDA	European Parkinson's Disease Association
EU	European Union
%F	percent fluctuation
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GCRC	good clinical research practice
GDPR	General Data Protection Regulation
GSH	glutathione
GSSG	glutathione disulfide
HDPE	high density polyethylene
hERG	human Ether-a-go-go Related Gene
HCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HMPAO	hexamethylpropylene amine oxime
ICF	informed consent form
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
λz	apparent terminal constant

LFT	liver function test
MAD	multiple ascending (oral) dose
MADRS	Montgomery and Asberg Depression rating scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
mg	milligram
mL	milliliter
MoCA	Montreal Cognitive Assessment
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPV	mean platelet volume
mtDNA	mitochondrial DNA
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NF	National Formulary
nM	nanomolar
NMSS	Non-motor Symptoms Scale
NOAEL	no observed adverse effect level
NQ01	NAD(P)H Quinone oxidoreductase 1
OD	once daily
OTC	over-the-counter
PD	Parkinson’s disease
PDQ-39	39-Item Parkinson’s Disease Questionnaire
PO	by mouth
PT	Prothrombin Time
PTT	Partial Prothrombin 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
SAD	single ascending (oral) dose
SAE	serious adverse event
SD	standard deviation
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

XIII. SIGNATURE OF SPONSOR

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 CPR 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: /a Sc 261 J Signature: [redacted]

[redacted]
Edison Pharmaceuticals, Inc.
350 North Bernardo Ave
Mountain View, CA 94043

XIV. REFERENCES

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Summary of Changes

Amendment 1.0

EPI589-15-002

A Phase 2A Safety and Biomarker Study of EPI-589 in Mitochondrial Subtype and Idiopathic Parkinson's Disease Subjects

Protocol Number	EPI589-15-002
Original Protocol Date	27 April 2015
Amendment 1.0 Date	09 September 2015
Study Sponsor	Edison Pharmaceuticals, Inc. 350 North Bernardo Avenue Mountain View, CA 94043
Sponsor's Representative	[redacted] Edison Pharmaceuticals, Inc. 350 North Bernardo Avenue Mountain View, CA 94043

KEY CHANGES TO THE PROTOCOL

Amendment 1 provides the following changes and their rationales:

Change	Rationale
Study title, objectives, and endpoints were modified	Primary endpoint has become safety as assessed by drug-related AEs, and biomarker assessments have become secondary endpoints.
CNS and urine biomarker assessments added	Glutathione will be measured in cerebral spinal fluid and urine as well as in blood.
DaTscan removed from Month-3 visit	Minimal anticipated measurable changes within the short 90-day treatment period do not warrant the radiation exposure of a second study-required DaTscan.
The Columbia Suicide Severity Scale has been added to the clinical safety assessments	FDA-DNP determination that assessments of suicidality be included in clinical trials of drugs for neurological indications.
DNA genetic analysis has been removed from Screening assessments	Specific testing for Parkinson's genetic subtypes is not necessary as a study procedure requirement.
Mattis Dementia Rating Scale has been removed from the efficacy variables	To minimize redundancy and responder burden.

DESCRIPTION OF CHANGES TO THE PROTOCOL

Relevant point changes to the protocol by section appear in the table below. Other changes that are informational in nature and do not involve implementation of new procedures, may not be individually identified, but the modified text appears in the protocol (see appropriate sections of interest). These changes may include administrative updates, clarifications, corrections, and editorial adjustments to improve clarity and provide consistency. Global changes appearing in multiple places throughout protocol may not be identified individually unless they appear within the context of other important changes.

In this summary document, ***bold italic*** font indicates additions to existing text, and ~~strikethrough~~ font indicates deleted text. The actual amended protocol does not include bold or strikethrough font to indicate changes.

<table>
<tr><th>Protocol Section</th><th>Modification (or Explanation)</th></tr>
<tr><td>Cover page; Synopsis; II.F</td><td>A Phase 2A ***Safety and*** Biomarker Study of EPI-589 in ***Mitochondrial Subtype and Idiopathic*** Parkinson's Disease ***Subjects***</td></tr>
<tr><td>Synopsis</td><td>Synopsis sections were updated to reflect all changes in the body of the protocol.</td></tr>
<tr><td>I Schedule of Assessments</td><td>
<table>
<tr><th rowspan="2">Tests</th><th colspan="2">-2 to -1 Months</th><th>Day 0</th><th>Month 1</th><th>Month 2</th><th>Month 3
End of Study</th></tr>
<tr><th>Screening</th><th>Run-in
(± 30 days)</th><th>Baseline</th><th>Day 29
(± 3 days)</th><th>Day 57[f]
(± 3 days)</th><th>Day 85
(± 3 days)</th></tr>
<tr><td>~~Genetic analysis~~[e]C-SSRS</td><td>✓[e]</td><td></td><td>✓</td><td>✓</td><td></td><td>✓</td></tr>
<tr><td>Montreal Cognitive Assessment</td><td>✓</td><td></td><td></td><td></td><td></td><td>✓</td></tr>
<tr><td>~~DaTscan~~</td><td>✓</td><td></td><td></td><td></td><td></td><td>~~✓~~</td></tr>
<tr><td>~~MRI & MRS~~</td><td></td><td>~~✓~~</td><td></td><td></td><td></td><td>~~✓~~</td></tr>
<tr><td>~~Glutathione~~Blood-based glutathione cycle biomarkers</td><td></td><td>✓</td><td>✓</td><td>✓</td><td></td><td>✓</td></tr>
<tr><td>Lumbar puncture</td><td></td><td>✓</td><td></td><td></td><td></td><td>✓</td></tr>
<tr><td>Urine-based biomarkers</td><td></td><td>✓</td><td>✓</td><td>✓</td><td></td><td>✓</td></tr>
<tr><td>MDS-UPDRS</td><td></td><td>✓</td><td>✓</td><td>✓</td><td></td><td>✓</td></tr>
<tr><td>Timed motor tests (for subjects on dopamine therapy)</td><td></td><td>✓</td><td>✓</td><td></td><td></td><td>✓</td></tr>
<tr><td>NMSS, PDQ-39, EQ-5D</td><td></td><td></td><td>✓</td><td></td><td></td><td>✓</td></tr>
<tr><td>DRS-2, BDI, MADRS</td><td></td><td></td><td>✓</td><td></td><td></td><td>✓</td></tr>
</table>
~~e. Subject should have genetic testing for PD genetic subtypes at screening if not done previously.~~
</td></tr>
<tr><td>II.B</td><td>EPI-589 is a redox active molecule that has demonstrated potency (EC50 <100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with ~~sporadic~~ ***idiopathic*** and familial PD genetic subtypes including PINK1, parkin and LRRK2.</td></tr>
<tr><td>III.A</td><td>A. Primary ~~Efficacy~~ Objective
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*** ~~on blood based glutathione cycle biomarkers~~ in subjects with PD.</td></tr>
<tr><td>III.B, III.C</td><td>B. Secondary Objectives
The secondary objectives are to evaluate the effects of EPI-589 in subjects with PD on:</td></tr>
</table>

	1. ~~Central nervous system (CNS)~~Glutathione cycle biomarkers as ~~assessed by magnetic resonance spectroscopy (MRS)~~***measured in blood, cerebral spinal fluid, and*** ~~DaTscan~~***urine*** 2. Clinical ~~D~~***d***isease ~~S~~***s***tate as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) 3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D ***4.*** Cognitive function as assessed by Montreal Cognitive Assessment (MoCA) ~~and Mattis Dementia rating scale (DRS-2)~~ 5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery & Asberg Depression rating scale (MADRS) 6. Pharmacokinetics ~~C. Safety Objectives~~ ***7.*** ~~To examine the safety of EPI 589 in subjects with PD by examining hematology h~~ ***H***ematology***, blood chemistry, electrocardiogram*** ~~, and drug-related AEs and SAEs~~.
IV.A2	Once eligibility is confirmed, the subject will be enrolled in the study and the run-in scans, ***CNS, blood-based*** biomarker***, urine-based biomarker*** and clinical measurements will be collected.
IV.A3	Baseline assessments, scans, ***blood-based*** biomarker, ***urine-based biomarker,*** and clinical measurements will be collected.
IV.A4	***Blood-based*** biomarker, ***urine-based biomarker,*** and clinical measurements will be collected at Day 29 (± 3 days) and Day 85 (± 3 days).
V.A	~~9. Genetic analysis for subjects that have not had prior genetic testing for PD mutations (See Section VI.D3.c)~~
V.A1	1. ***Blood-based G***lutathione cycle biomarkers ***2. CNS biomarkers*** ***3. Urine biomarkers*** 4. MDS-UPDRS 5. Timed motor tests (for subjects on dopamine therapy) 6. Concomitant medications review
V.B1	The following will be assessed or performed at this visit. 1. Physical examination including vital signs 2. Height and weight* 3. 12-Lead ECG* 4. ***Blood-based*** GSH cycle biomarkers 5. ***Urine-based biomarkers*** 6. Laboratory assessments for hematology, coagulation and serum chemistry* 7. Urine pregnancy test (females of child bearing potential) ***8. C-SSRS (Columbia Suicide Severity Rating Scale)*** 9. MDS-UPDRS 10. NMSS, PDQ-39, EQ-5D ~~11. DRS 2~~ BDI, MADRS

	11. Timed motor tests (for subjects on dopamine therapy) 12. Concomitant medications review
V.B2	The following will be assessed or performed at the Month 1 clinic visit: 1. Physical examination including vital signs 2. Height and weight 3. 12-lead ECG 4. Laboratory assessments for hematology, coagulation, and serum chemistry 5. Urine pregnancy test (females of child bearing potential) ***6. C-SSRS*** 7. ***Blood-based*** GSH cycle biomarkers 8. ***Urine-based biomarkers*** 9. MDS-UPDRS 10. Pharmacokinetics: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing. 11. AE assessments 12. Concomitant medications review
V.B2	The following will be assessed or performed at the Month 3 clinic visit: 1. Physical examination including vital signs 2. Height and weight 3. 12-lead ECG 4. Laboratory assessments for hematology, coagulation, and serum chemistry 5. Urine pregnancy test (females of child bearing potential) ***6. C-SSRS*** 7. ***Blood-based*** GSH cycle biomarkers 8. ***Urine-based biomarkers*** ***9. CNS biomarkers*** 10. MDS-UPDRS 11. Pharmacokinetics: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing. 12. AE assessments 13. Concomitant medications review ~~14. MRI and MRS~~ ~~15. DaTscan~~ 14. MoCA 15. NMSS, PDQ-39, EQ-5D ~~16. DRS 2~~ 16. BDI, MADRS 17. Timed motor tests (for subjects on dopamine therapy)
VI. A	A. Primary ~~Efficacy~~ Endpoint ~~Change from baseline in blood based glutathione cycle biomarkers in subjects with PD.~~ To evaluate the effects of EPI-589 on safety as assessed by occurrence of drug-

	related serious adverse events in subjects with PD.
VI. B	**B. Secondary ~~Efficacy~~ Endpoints *(Efficacy)*** ***1. Blood-based biomarkers*** ***2. CNS-based biomarkers*** 3. ~~MRS, DaTscan~~ **3.** ***Urine-based biomarkers*** 4. MDS-UPDRS 5. NMSS 6. PDQ-39 7. EQ-5D ~~8. DRS-2~~ 8. MoCA 9. BDI 10. MADRS 11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy) ***12. Pharmacokinetics***
VI.C	**C. ~~Safety~~ *Secondary* Endpoints *(Safety)***
VI.D3.c	~~**c. DNA sample**~~ ~~1. 1.5 mL EDTA blood sample for DNA extraction for genetic testing for PD subtypes at screening if not done previously.~~
VI.D4	~~D.4 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.***
VI.E	~~Fasting b~~***B***lood***, urine, and cerebral spinal fluid*** samples will be collected for determination of levels of GSH cycle markers. ~~A contract laboratory will receive samples via courier in order to test GSH cycle components and to perform the pharmacokinetic analysis.~~ Additional information about the collection, handling, storage, and shipment of the GSH cycle marker samples will be provided separately prior to start of the study. ~~Blood samples for clinical laboratory measurements should be collected and processed according to the site's laboratory's standard procedure.~~
VI.F1	**Blood, urine, *and CNS*** levels of oxidized and reduced GSH as well as GSH metabolites will be used to evaluate EPI-589 target engagement and ability to correct a key biochemical aspect of disease pathology.
~~VI.F2~~	~~MRS will be used to measure GSH and other metabolites in the basal ganglia. Extent of cortical and basal degeneration will be assessed by MRI. Dopamine uptake will be measured by DaTscan.~~
VI.F.8	~~*F8. Mattis Dementia Rating Scale (DRS-2)*~~ ~~The DRS-2 is an instrument used in screening for dementia designed for adults with cognitive impairment aged 56 and older. It provides a composite score and five subscale scores in Attention, Initiation Perseveration, Construction, Conceptualization, and Memory.~~
VII.A	In this ~~a within~~ subject~~,~~ ~~c~~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.
VII.B1 VII.B2	~~*B1. Primary Efficacy Variables*~~ ~~The primary efficacy variable is GSH cycle biomarkers (at baseline, Day 29 and Day 85).~~ *B1~~B.2 Secondary~~ Efficacy ~~Endpoints~~ Variables* ***1. Blood-based glutathione cycle biomarkers*** ***2. CNS biomarkers*** ***3. Urine-based biomarkers*** 4. ~~Brain MRS, DaTscan~~ 4. MDS-UPDRS 5. NMSS 6. PDQ-39 7. EQ-5D 8. MoCA ~~9. DRS-2~~ 9. BDI 10. MADRS 11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy) ***12. Pharmacokinetics***
VII.C.	***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 PD.*** 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.
VII.D	Approximately 40 subjects (20 with genetically-defined subtypes of PD and 20 PD drug-naïve subjects). ***Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects.***
XII	**XII. LIST OF ABBREVIATIONS** *C-SSRS* | *Columbia-Suicide Severity Rating Scale*

End of Document

####

EPI589-15-002

A Phase 2A Biomarker Study of EPI-589 in Subjects with Parkinson's Disease

Original Protocol: 27 April 2015

Edison Pharmaceuticals, Inc.
350 North Bernardo Avenue
Mountain View, CA 94043

Table of Contents

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PROTOCOL SYNOPSIS

Title of study	A Phase 2A Biomarker Study of EPI-589 in Subjects with Parkinson's Disease
Protocol number	EPI589-15-002
IND number	TBD
EudraCT number	2015-001786-10
Investigative Drug	EPI-589
Study Sponsor	Edison Pharmaceuticals Inc. 350 North Bernardo Avenue Mountain View, CA 94043
Investigators and Investigative Sites	• [redacted] USA • [redacted] UK
Study population	Approximately 40 subjects with Parkinson's disease (PD) including 20 subjects with genetically-defined subtypes
Rationale for Study	<u>Mitochondrial pathophysiology</u> It is now well appreciated that defects in mitochondrial function contribute to the pathophysiology of PD both in subjects with defined genetic defects as well as those with idiopathic forms of the disease. <u>High morbidity</u> Despite the available therapies for symptomatic relief, PD remains a highly morbid disease. There are no approved treatments for PD capable of modifying disease progression. <u>Pre-clinical efficacy data</u> EPI-589 is a redox active molecule that has demonstrated potency (EC50 < 100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with sporadic and familial PD subtypes including PINK1, parkin and LRRK2.
Study objectives	<u>Primary Efficacy Objective</u> To evaluate the effects of EPI-589 on blood-based glutathione cycle biomarkers in subjects with PD.

	Secondary Efficacy Objectives To evaluate the effects of EPI-589 in subjects with PD on: 1. Central nervous system (CNS) biomarkers as assessed by magnetic resonance spectroscopy (MRS) and DaTscan 2. Clinical Disease State as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) 3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D 4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA) and Mattis Dementia rating scale (DRS-2) 5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery and Asberg Depression rating scale (MADRS) 6. Pharmacokinetics Safety Objectives To examine the safety of EPI-589 in subjects with PD by examining hematology, blood chemistry, electrocardiogram, and drug-related adverse events (AEs) and serious adverse events (SAEs).
Study design	Open-label study with 30-day run-in phase and adaptive design component to include more subjects if deemed appropriate by investigators.
Planned number of subjects	Approximately 40 subjects (20 with genetically-defined subtypes of PD and 20 drug-naïve idiopathic PD subjects).
Study duration	3 months of study treatment preceded by a 1-month baseline parameter run-in period.
Test product, mode of administration, and dose	Test product EPI-589 in a tablet formulation at a strength of 250 mg Mode of Administration Oral with meal Dose EPI-589 500-mg BID

Reference therapy, dose, and mode of administration	None
Safety monitoring	Clinical 1. Physical exam and vital signs 2. Evaluation of adverse events 3. 12-lead Electrocardiogram Laboratory 1. Routine serum chemistries 2. Routine hematology tests and coagulation tests
Inclusion criteria	1. Hoehn and Yahr stage ≤ 2.5 2. Ambulatory with or without assistance 3. Agreement to use contraception if within reproductive years 4. Willingness and ability to comply with study procedures 5. Stable regimen of dietary supplements for 30 days prior to enrollment 6. Abstention from use of other investigative or non-approved drugs for the duration of the trial *For Idiopathic Subjects* 7. *For idiopathic subjects*: a diagnosis of early idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit 8. *For idiopathic subjects*: must not yet require symptomatic medications for PD and not expected to require such treatment before the end of the study 9. *For idiopathic subjects*: age 40 to 75 years 10. *For idiopathic subjects*: within 5 years of diagnosis of Parkinson's disease *For Genetic Subtype Subjects* 11. *For genetic subtype subjects*: a confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LARK2 or other mitochondrial genetic subtype

12. *For genetic subtype subjects*: age 21 to 75 years
13. *For genetic subtype subjects*: stable medication regimen of PD drugs for 30 days (except 60 days for rasagiline) prior to enrollment

Exclusion criteria

1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation
2. Use of antioxidant supplements, specifically vitamins E and C beyond the recommended daily allowance
3. Other Parkinsonian disorders
4. MoCA score of <24
5. Revised Hamilton Rating Scale for Depression ≥ 11
6. Parkinsonism due to drugs or toxins
7. Diagnosis of any other clinically significant neurologic disease that will confound the assessment of effect of study drug on disease progression
8. Malignancy within past two years
9. Pregnant or plans to become pregnant or breast feeding
10. History of stroke
11. History of brain surgery
12. Hepatic insufficiency with liver function tests (LFTs) > 3 times upper limit of normal
13. Renal insufficiency as defined by creatinine > 1.5 times normal
14. End stage cardiac failure
15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD

For Idiopathic Subjects

16. *For idiopathic subjects*: use of any MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease for idiopathic subjects
17. *For idiopathic subjects*: use of nortriptyline or fluvoxamine 60 days prior to enrollment

Treatment

Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months unless

	discontinued for safety or tolerability issues. Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects.
Efficacy variables	1. Blood-based glutathione biomarkers 2. Brain MRS, DaTscan 3. MDS-UPDRS 4. Non-motor Symptoms Scale (NMSS) 5. PDQ-39 6. EQ-5D 7. Montreal Cognitive Assessment (MoCA) 8. Mattis Dementia rating scale (DRS-2) 9. Beck Depression Inventory (BDI) 10. Montgomery & Asberg Depression rating scale (MADRS) 11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)
Safety variables	Clinical 1. Routine assessments of AEs and SAEs 2. Dose limiting toxicities 3. Electrocardiogram Laboratory 1. Routine serum chemistries with liver function tests 2. Routine hematology tests with coagulation tests
Statistical Considerations	<u>Data Analysis</u> This is a within-subject, controlled open-label study seeking to determine if EPI-589 can alter the biochemical signature of PD as assessed by peripheral blood biomarkers and brain imaging biomarkers. In addition, data on a number of disease-relevant clinical measures will be collected.

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I. SCHEDULE OF ASSESSMENTS AND DOSING SCHEDULE

Tests	-2 to -1 Months		Day 0	Month 1	Month 2	Month 3 End of Study
	Screening	Run-in (± 30 days)	Baseline	Day 29 (± 3 days)	Day 57[e] (± 3 days)	Day 85 (± 3 days)
Informed consent	✓					
Inclusion/Exclusion criteria	✓					
Past Medical history	✓					
Previous genetic testing review	✓					
Physical exam & Vital signs	✓		✓	✓		✓
Height & weight	✓		✓[a]	✓		✓
12-lead ECG	✓		✓[a]	✓		✓
Hematology (including coagulation panel)	✓		✓[a]	✓		✓
Serum Chemistry	✓		✓[a]	✓		✓
Pregnancy test[b]	✓		✓	✓		✓
Genetic analysis[c]	✓[c]					
Montreal Cognitive Assessment	✓					✓
DaTscan	✓					✓
Revised Hamilton Rating Scale for Depression	✓					
Subject enrolls in study		X				
MRI & MRS		✓				✓
Glutathione cycle biomarkers		✓	✓	✓		✓
MDS-UPDRS		✓	✓	✓		✓
Timed motor tests (for subjects on dopamine therapy)		✓	✓			✓
NMSS, PDQ-39, EQ-5D			✓			✓
DRS-2, BDI, MADRS			✓			✓
Drug plasma concentration[d]				✓[d]		✓[d]
AE/SAE assessment				✓	✓[e]	✓[e]
Concomitant medications assessment	✓	✓	✓	✓	✓[e]	✓[e]

a. Screening values can be used if done within one month of baseline.
b. Female subjects of childbearing potential must have a negative pregnancy test.
c. Subject should have genetic testing for PD genetic subtypes at screening if not done previously.
d. Full plasma concentration profile will be obtained at Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing from the first 10 subjects to complete 1 month of therapy at each site.
e. Month 2 assessments can be done by telephone. Any new AEs and associated concomitant medications reported at Month 3 must be followed for 30 days; this follow up may be conducted by telephone.

Dosing Schedule				Month 1	Month 2	Month 3
EPI-589 500-mg BID				✓	✓	✓

II. BACKGROUND INFORMATION AND RATIONALE

A. Introduction

Parkinson's disease (PD) is a highly morbid neurodegenerative movement disorder that has a number of neuromuscular, cognitive and neuropsychiatric manifestations as well as non-neurological symptoms. PD is the second most common neurodegenerative disorder with an estimated prevalence of 6.3 million people worldwide (EPDA).

PD has long been considered a non-genetic (idiopathic) disease; however, about 5% of patients have an identifiable mutation. Disease onset typically occurs after age 50, however, in a subset of patients, disease onset can occur at a younger age. The primary motor symptoms result from death of dopamine-producing cells in the pars compacta region of the substantia nigra. However, the mechanisms underlying this cell death and disease pathology remain poorly understood. There is no approved treatment for PD capable of modifying disease progression. Current therapies partially address disease motor symptoms through levodopa or dopamine agonists or other agents, and other disease symptoms (e.g. neuropsychiatric symptoms), but disability tends to increase over time despite these treatments.

The association of PD with mitochondrial pathology and high levels of oxidative stress are well established. Increased levels of oxidative stress have been consistently measured in post-mortem specimens from PD patients (Maarouf 2012, Reale 2012). The occurrence of PD-like symptoms in heroin addicts exposed to MPTP in the 1980s established a first link between PD and mitochondrial injury (Langston 1983, Dauer and Przedborski 2003). MPTP inhibits complex 1 of the mitochondrial respiratory chain and induces degeneration of dopaminergic cells through oxidative stress-mediated injury. The link between mitochondrial injury and PD was further strengthened by the induction of PD symptoms following exposure to another neurotoxic complex 1 inhibitor, rotenone (Betarbet et al 2000, Greenamyre et al. 2003), which like MPTP has come to be used in pre-clinical testing for its phenotypic similarities to PD.

Furthermore, the identification of genetic mutations such as PINK1, parkin, LRRK2 and others in mitochondrial genes in familial PD patients provided the strongest link between the mitochondria and PD (Winklhofer and Haass 2010). Normally these genes influence oxidative balance and provide neural protection of the dopaminergic neurons that are affected by PD. PINK1 and parkin are involved in protecting against oxidative stress (OS) and overabundant reactive oxygen species (ROS), and are implicated in cell morphology and dynamics, as well as in the preferential degradation of dysfunctional mitochondria or "mitophagy" (Ashrafi et al. 2014). Mutant LRRK2 leads to the accumulation of misfolding intracellular protein accumulations, cell stress and apoptosis (Giasson et al. 2006, Zhu et al. 2006).

The importance of oxidative stress in PD pathology is further substantiated by the measurement of decreased levels of reduced glutathione in the brains of patients with PD (Holmay et al. 2013). Glutathione levels are low at very early stages of PD and correlate with disease severity (Riederer et al. 1989), and experimental induction of glutathione depletion leads to mitochondrial complex I dysfunction (Jha et al, 2000;). Reduced glutathione is an essential intermediary

metabolite that serves as the primary native cellular antioxidant. In a state of high oxidative stress, elevated levels of ROS outstrip the supply of glutathione (GSH) resulting in depletion of GSH and ROS-mediated cell death.

Given the important role of oxidative stress and mitochondrial pathology in PD, a redox-active therapy that could target key pathways in cellular OS response pathways may hold promise for the treatment of PD.

B. Rationale for the Study of EPI-589 in Parkinson's Disease

EPI-589 is a redox active molecule that has demonstrated potency (EC50 <100nM) and efficacy (>80% rescue from oxidative stress-induced cell death) in cells derived from patients diagnosed with sporadic and familial PD genetic subtypes including PINK1, parkin and LRRK2.

In these cell-based assays, primary fibroblasts from patients (and control) were pre-incubated with and without test compound, then treated with L-buthionine-(S,R)-sulfoximine (BSO), a GSH synthesis inhibitor, to initiate depletion of cellular GSH. GSH depletion has been shown to lead to OS and disruption of calcium homeostasis resulting in loss of the mitochondrial membrane potential and cell death. Under these conditions, the control cells are resistant to the stress and the fibroblast cells from patients with disease indications die within 36 to 48 hours. Pretreatment of cells with EPI-589 prior to initiation of GSH depletion potently protected against oxidative stress-mediated cell death, with EC_{50} response concentrations of 16 to 52 nM.(Table 1).

Table 1: Cell Line Rescue with EPI-589 in Parkinson's Disease Genetic Subtypes

	EPI-589 **EC_{50} (nM range)**
PINK1	26-36
LRRK2	16-18
parkin	42-52

C. Name and Description of Investigational Product

The IUPAC name of 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 derived from resolved (R)-Trolox®, a derivative of vitamin E in the form of a pale yellow to yellow solid. The EPI-589 drug product will be provided in a 250-mg tablet formulation.

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. In 28-day and 91-day repeat-dose toxicity studies in rat and cynomolgus monkey, the no observed adverse effect level (NOAEL) was 300 mg/kg/day, corresponding to combined mean Cmax values of 37,717 to 56,500 ng/mL (rat) and 14,300 to 16,417 ng/mL (monkey), and a combined mean area under the plasma concentration-time curve from time zero to the last measurable concentration (AUClast) value of 149,495 to 297,000 ng.h/mL (rat) and 47,300 to 67,656 ng.h/mL (monkey) (Studies 1660-038, 1660-039, 1660-063, and 1660-064).

A phase 1 clinical study demonstrated that healthy subjects administered 500 mg EPI-589 BID for 14 days showed a mean Cmax value of 1,890 ng/mL and a mean AUClast value of 5,240 ng.h/mL (Study EPI589-14-01). These plasma concentrations are well below the mean exposure values in monkey associated with the NOAEL in the toxicity studies, corresponding to safety margins of approximately 7- to 8-fold for the mean Cmax and 9- to 12-fold for the mean AUC.

During the 28-day repeat-dose toxicity studies, rat and monkey were exposed to up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-039 and 1660-038). The NOAEL for both studies was 300 mg/kg/day. Rats exposed to 1,000 mg/kg/day exhibited adverse 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 showing corresponding microscopic pathology. The majority of these findings were resolved following the 28-day recovery period. Monkeys exposed to 1,000 mg/kg/day showed significant test-article related morbundidity that resulted in half the animals in the high dose group being euthanized on Days 3 and 4 and the remaining animals being euthanized on Day 9. These animals exhibited significant elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values, and microscopic findings in the kidney, liver, skeletal muscle, heart, and lymphoid tissues. In several of the animals the primary cause of morbidity was determined to be test-article related renal tubular degeneration/necrosis.

During the 91-day repeat-dose toxicity studies, rat and monkey were exposed to up to 300 mg/kg/day EPI-589 PO (Studies 1660-063 and 1660-064). The NOAEL for the rat study was 300 mg/kg/day and the no observed effect level (NOEL) for the monkey study was 300 mg/kg/day. [redacted] rats exposed to 300 mg/kg/day and [redacted] rats exposed to ≥ 100 mg/kg/day exhibited mild test-article related effects on hematology parameters consistent with hemolysis and bone marrow regeneration. These findings were not considered adverse.

Development and reproductive toxicology studies were conducted in rat and rabbit at doses up to 1,000 mg/kg/day EPI-589 PO (Studies 1660-069, 1660-067, and 1660-068). The NOAEL for reproductive toxicity in rat was demonstrated to be 1,000 mg/kg/day (1660-069). The NOAEL

for developmental toxicity in rat and rabbit during the embryofetal studies was deemed to be 300 mg/kg/day (Studies 1660-067 and 1660-068). Rats exposed to 1,000 mg/kg/day exhibited 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. Rabbits exposed to 1,000 mg/kg/day exhibited 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 (Study EPI589-14-01) and rabbits exposed to 1,000 and 300 mg/kg/day EPI-589 is approximately 179- to 236-fold and 47- to 50-fold, respectively. 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 (Study AD58AS.502ICH.BTL); 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 (Study AD58AS.331ICH.BTL); and negative in the in vivo micronucleus assay in rat (Study AD58AS.125012ICH.BTL). These data indicate a low clinical mutagenicity risk.

Primary pharmacodynamics studies demonstrated that EPI-589 is a potent rescue agent in cellular models of diseases of energy metabolism and oxidative stress. In vitro cellular models utilizing primary human fibroblasts from patients with ALS, Parkinson's disease and other diseases characterized by high levels of oxidative stress, or striatal cells derived from mouse models of Huntingdon's disease were used to assess the potential of EPI-589 to mitigate the harmful effects of oxidative stress (Studies EPI-BA-000216, EPI-BA-000363, and EPI-BA-000362). Pretreatment of patient cells with EPI-589 potently protected against oxidative stress-mediated cell death in a concentration dependent manner. Furthermore, EPI-589 normalized 3-nitrosotyrosine (3NT) levels, a biomarker of oxidative stress, and increased glutathione levels in mouse striatal cells under oxidative stress conditions.

In secondary pharmacodynamics in vitro receptor/ion channel binding studies, EPI-589 did not significantly affect off-target molecular targets (Study EPI-BA-159). In safety pharmacology studies, EPI-589 did not significantly affect ion channel current in the hERG assay (Study 130719.FEK); did not affect ECG parameters during the 28-day and 3-month repeat-dose toxicology studies in monkey at doses up to 1,000 mg/kg/day (only Day 1 data collected for animals administered 1,000 mg/kg/day and up to Day 91 data collected for animals administered up to 300 mg/kg/day) (Studies 1660-038 and 1660-064); and did not change respiratory function or adversely impact neurobehavioral function in rat at doses up to 1,000 mg/kg (Studies 1660-051, 1660-050, and 1660-063).

In single dose exposure PK studies, EPI-589 was absorbed rapidly in rat, dog, and monkey, with mean Tmax values ranging from .08 to 1 hour and mean T1/2 values ranging from 3.7 to 5.0 hours (Studies EPI-BA-53, EPI-BA-59, EPI-BA-72, and EPI-BA-302). EPI-589 does not significantly induce cytochrome P450 (CYP) enzymes and appears to be metabolized by

reductases in the liver cytosol and microsomal subcellular fractions and to a lesser extent by the family of CYP enzymes (Studies MC12M-0037 and MC14M-0018).

EPI-589 exhibited weak direct inhibition of CYP2B6, CYP2C8, CYP2C9, and CYP3A4/5 (both midazolam and testosterone as probe substrates) with estimated IC_{50} (μM) values and R values based on free plasma concentrations (shown in parentheses) of 28 (1.25), 40 (1.18), 92 (1.08), 34 (1.21), and 53 (1.13), respectively (Study MC14M-0020)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.

D2. Clinical Studies

Phase I Study EPI589-13-022 evaluated the pharmacokinetics, safety and tolerability of single ascending oral doses (SADs) of EPI-589 in healthy subjects and a preliminary evaluation of safety and tolerability data was performed. Sixteen AEs were reported in the 36 subjects who received administration of EPI-589. Ten subjects (27.8%) who received EPI-589 (and 2 subjects, 20% on placebo) reported AEs that were assessed as related. All were mild and resolved during the study, with the exception of a common cold (1 subject) and cold sore (1 subject). 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. Twenty-six subjects (65.0%) on EPI-589, and 8 subjects (80%) on placebo reported AEs. Twenty-four of 34 AEs were considered by the Investigator to be related to EPI-589. Nineteen subjects (47.5%) on EPI-589, and 6 subjects (60%) on placebo reported AEs that were assessed as related. All adverse events were mild, except for 1 AE which was moderate (unrelated brain contusion). All AEs were resolved during the study, with the exception of one, which was a common cold. 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 the MAD study it may be concluded that there is no objection to proceed with treatment with 250-mg, or 500-mg doses of EPI-589.

E. Human Pharmacokinetics

EPI-589 was fast absorbed following oral administration in SAD Study EPI589-13-022. The median C_{max} was attained approximately within 1 hour under fasted conditions after dosing. The median T_{max} values were attained in 0.50 to 1.00 hours over the dose range of 50 to 1000 mg under fasted conditions and 3.01 hours at the 500 mg dose level under fed conditions. Mean half-life ranged from 5.55 to 10.7 hours over the dose range of 50 to 1000 mg under fasted conditions and 4.91 hours at the 500 mg dose level under fed conditions. Half-life was independent of the dose levels over the dose range of 50 to 1000 mg under fasted conditions. The rate of EPI-589 absorption, as measured by C_{max}, was decreased by 24.07% under fed conditions at the 500 mg

dose level. The extent of absorption as measured by AUCs (AUC_{0-t} or AUC_{0-inf}) was not affected under fed conditions in the 500 mg dose groups.

In MAD study EPI589-14-01, 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 of various ages and smoking status. No significant effects of age or smoking on EPI-589 pharmacokinetics were observed in this study. Dose proportionality existed in the exposures (AUC_{0-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

EPI589-15-002: A Phase 2A Biomarker Study of EPI-589 in Subjects with Parkinson's Disease.

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 meals.

H. Compliance Statement

This study will be conducted in full accordance with all applicable research policies and procedures, the EU Clinical Trials Directive, all applicable EU and 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, will obtain consent and will 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.

I. Relevant Literature and Data

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

III. STUDY OBJECTIVES

A. Primary Efficacy Objective

The primary objective of this study is to evaluate the effects of EPI-589 on blood-based glutathione cycle biomarkers in subjects with PD.

B. Secondary Objectives

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

1. Central nervous system (CNS) biomarkers as assessed by magnetic resonance spectroscopy (MRS) and DaTscan
2. Clinical Disease State as assessed by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
3. Disease morbidity as assessed by the Non-motor Symptoms Scale (NMSS), PDQ-39 and EQ-5D
4. Cognitive function as assessed by Montreal Cognitive Assessment (MoCA) and Mattis Dementia rating scale (DRS-2)
5. Mood as assessed by the Beck Depression Inventory (BDI) and the Montgomery & Asberg Depression rating scale (MADRS)
6. Pharmacokinetics

C. Safety Objectives

To examine the safety of EPI-589 in subjects with PD by examining hematology, blood chemistry, electrocardiogram, and drug-related AEs and SAEs.

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IV. INVESTIGATIONAL PLAN

A. General Schema of Study Design

Following study enrollment, baseline assessments will be performed. Subjects will participate in a 30-day run-in phase to establish biomarker and clinical baseline measurements. EPI-589 will then be administered for up to 3 months unless discontinued for safety or tolerability issues.

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects.

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 run-in scans, biomarker and clinical measurements will be collected.

A3. Baseline

Baseline assessments, scans, biomarker 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.

Scans, biomarker and clinical measurements will be collected at Day 29 (± 3 days) and Day 85 (± 3 days).

A5. End of Study

End of study data will be collected at the last study visit Day 85 (± 3 days).

AEs reported as ongoing at Day 85, any associated concomitant medications associated with such events, and any events occurring within 30 days of last dose will be followed for 30 days.

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 biomarker and clinical baseline measurements. EPI-589 will then be administered for 3 months unless discontinued for safety or tolerability issues.

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

This study will be conducted at two study sites:

- [redacted] UK
- [redacted] USA.

Approximately 40 subjects with PD are projected:

- 20 with genetically-defined subtypes
- 20 PD drug-naïve

Under an adaptive design strategy, additional subjects (up to 20) may be added to increase the number of biomarker responsive idiopathic PD subjects.

D. Study Population

D1. Inclusion Criteria

1. Hoehn and Yahr stage ≤ 2.5
2. Ambulatory with or without assistance
3. Agreement to use contraception if within reproductive years
4. Willingness and ability to comply with study procedures
5. Stable regimen of dietary supplements for 30 days prior to enrollment
6. Abstention from use of other investigative or non-approved drugs for the duration of the trial

For Idiopathic Subjects

7. *For idiopathic subjects*: a diagnosis of early idiopathic PD confirmed by the presence of bradykinesia plus one or both of the following symptoms: rigidity or resting tremor; and with an abnormal DaTscan consistent with a dopaminergic deficit
8. *For idiopathic subjects*: must not yet require symptomatic medications for PD and not expected to require such treatment before the end of the study
9. *For idiopathic subjects*: age 40 to 75 years
10. *For idiopathic subjects*: within 5 years of diagnosis of Parkinson's disease

For Genetic Subtype Subjects

11. *For genetic subtype subjects*: a confirmed diagnosis of PD plus a genetic diagnosis consistent with PD, specifically PINK1, parkin, LARK2 or other mitochondrial genetic subtype
12. *For genetic subtype subjects*: age 21 to 75 years
13. *For genetic subtype subjects*: stable medication regimen of PD drugs for 30 days (except 60 days for rasagiline) prior to enrollment

D2. <u>Exclusion Criteria</u>

1. Allergy to EPI-589 or other components of the EPI-589 tablet formulation
2. Use of antioxidant supplements, specifically vitamins E and C beyond the recommended daily allowance
3. Other Parkinsonian disorders
4. MoCA score of <24
5. Revised Hamilton Rating Scale for Depression ≥ 11
6. Parkinsonism due to drugs or toxins
7. Diagnosis of any other clinically significant neurologic disease that will confound the assessment of effect of study drug on disease progression
8. Malignancy within past two years
9. Pregnant or plans to become pregnant or breast feeding
10. History of stroke
11. History of brain surgery
12. Hepatic insufficiency with liver function tests (LFTs) > 3 times upper limit of normal
13. Renal insufficiency as defined by creatinine > 1.5 times normal
14. End stage cardiac failure
15. Participation within past 3 months and for duration of study in a trial of a device, drug or other therapy for PD

For Idiopathic Subjects

16. *For idiopathic subjects*: use of any MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease for idiopathic subjects
17. *For idiopathic subjects*: use of nortriptyline or fluvoxamine 60 days prior to enrollment

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V. STUDY PROCEDURES

A. Screening Visit

Screening evaluations will be performed within two months of first dose. The Investigator will inform each prospective subject of the nature of the study, explain the potential risks, and must 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. Receipt and review of previous testing including genetic tests
4. Physical examination including vital signs
5. Height and weight
6. 12-lead ECG
7. Laboratory assessments for hematology, coagulation, and serum chemistry (See Sections VI.D3.a and VI.D3.b)
8. Urine pregnancy test (women of childbearing potential must have a negative urine pregnancy test; see Section VI.D3.d)
9. Genetic analysis for subjects that have not had prior genetic testing for PD mutations (See SectionVI.D3.c)
10. MoCA
11. DaTscan
12. Revised Hamilton Rating Scale for Depression
13. Concomitant medications assessment (last 60 days prior to enrollment)

A1. Run-in Assessments

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 within one month for Run-in assessments. These will 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. Glutathione cycle biomarkers
2. MRI and MRS
3. MDS-UPDRS
4. Timed motor tests (for subjects on dopamine therapy)

5. Concomitant medications review

B. Treatment Phase

After the Run-in phase, the subject must return to the clinic within 30 days (± 3 days) for baseline assessments. In-clinic study visits are scheduled at Month 1 and Month 3. The Month 2 study assessments can be conducted via telephone. End of Study assessments will be conducted 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 including vital signs
2. Height and weight*
3. 12-Lead ECG*
4. GSH cycle biomarkers
5. Laboratory assessments for hematology, coagulation and serum chemistry*
6. Urine pregnancy test (females of child bearing potential)
7. MDS-UPDRS
8. NMSS, PDQ-39, EQ-5D
9. DRS-2
10. BDI, MADRS
11. Timed motor tests (for subjects on dopamine therapy)
12. Concomitant medications review

* Screening results for these assessments may be used if obtained within 1 month of Baseline.

B2. Study Visit Assessments

- Month 1 Clinic Visit (Day 29 ± 3 days):

The following will be assessed or performed at the Month 1 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry
5. Urine pregnancy test (females of child bearing potential)

6. GSH cycle biomarkers
7. MDS-UPDRS
8. Pharmacokinetics: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.
9. AE assessments
10. Concomitant medications review

- Month 2 Visit (Day 57 ± 3 days)

Month 2 assessments can be conducted by telephone and must include review of:

1. Concomitant medication
2. AEs

- Month 3 Clinic Visit (Day 85 ± 3 days)

The following will be assessed or performed at the Month 3 clinic visit:

1. Physical examination including vital signs
2. Height and weight
3. 12-lead ECG
4. Laboratory assessments for hematology, coagulation, and serum chemistry
5. Urine pregnancy test (females of child bearing potential)
6. GSH cycle biomarkers
7. MDS-UPDRS
8. Pharmacokinetics: a full plasma drug concentration profile will be obtained from the first 10 subjects to complete 1 month of therapy at each site at: Time = 0, and 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing.
9. AE assessments
10. Concomitant medications review
11. MRI and MRS
12. DaTscan
13. MoCA
14. NMSS, PDQ-39, EQ-5D
15. DRS-2
16. BDI, MADRS

17. Timed motor tests (for subjects on dopamine therapy)

B3. Pharmacokinetics

Plasma concentration samples will be collected from the first 10 subjects to complete 1 month of therapy at each site, at the following time points:

- Month 1 (Day 29 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose
- Month 3 (Day 85 ± 3 days): 0 hour and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose

B4. Early Termination Study Visit

Subjects who terminate from the study after receiving first dose and prior to the completion of all scheduled visits should have the end of study visit assessments completed as soon as possible.

C. End of Study Visit

End of Study visit takes place at Month 3 (Day 85 ± 3 days) and includes the assessments listed in Section VB2 Study Visit Assessments.

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 study visit windows, assessments will be made at the Investigator's discretion. All study relevant unscheduled visit assessments will be recorded in the case report form (CRF) using the supplemental visit CRF pages.

E. Concomitant Medication

Any medication taken by a subject ≤ 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 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 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 and for the duration of the study in a trial of a device, drug or other therapy for PD
3. Use of MAO inhibitors, amantadine or other drugs prescribed for core symptoms of Parkinson's disease for idiopathic subjects
4. Use of nortriptyline or fluvoxamine

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. At the specific request of the Sponsor (or designee)
4. 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 IX.B.

Evaluations should 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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VI. STUDY ENDPOINTS AND EVALUATIONS

A. Primary Efficacy Endpoint

Change from baseline in blood-based glutathione cycle biomarkers in subjects with PD.

B. Secondary Efficacy Endpoints

1. MRS, DaTscan
2. MDS-UPDRS
3. NMSS
4. PDQ-39
5. EQ-5D
6. MoCA
7. DRS-2
8. BDI
9. MADRS
10. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)

C. Safety Endpoints

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. Electrocardiogram

D. Screening and Baseline Evaluation

D1. Physical Examination

Complete physical exams will be conducted (excluding genital/rectal exam) at protocol specified study visits. 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, heart, abdomen, and extremities.

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).

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

D2. Height and Weight

Weight (kg) will be measured in ordinary indoor clothing (i.e., street clothes, scrubs, etc.) with shoes off. Height will be recorded in centimeters (cm).

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.

D3. Laboratory Evaluations

Subjects 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 I).

a. 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 (WBC) 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) with INR, partial thromboplastin time (PTT), activated (aPTT)

b. Serum chemistry

1. Liver: Alkaline Phosphatase (ALP), ALT (serum glutamic-pyruvic transaminase [SGPT]), AST (serum glutamic-oxaloacetic transaminase [SGOT]), bilirubin (total and direct), gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH)
2. Renal: blood urea nitrogen (BUN), and creatinine
3. Electrolytes: sodium, potassium, chloride, and carbon dioxide (CO2) as bicarbonate
4. General: creatine phosphokinase (CPK), creatine kinase (CK), and troponin (at baseline only); total protein, 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

c. DNA sample

1. 1.5 mL EDTA blood sample for DNA extraction for genetic testing for PD subtypes at screening if not done previously.

d. Urine pregnancy test

1. Human chorionic gonadotropin (HCG) beta subunit will be measured on all female subjects of childbearing potential.

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.

Diagnoses associated with any NIH Common Terminology Criteria for Adverse Events (CTC v4.03) Grade 3 or 4 laboratory abnormalities will be recorded as SAEs on the CRF. Repeated and verified $\geq$ Grade 3 laboratory tests will be reported as an SAE to the Sponsor and the IRB per institutional requirements. The recorded event 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.

E. Sample Collection Procedures, Bioanalytical Methods and Sample Shipment

Subject samples will be identified by unique sample codes.

Fasting blood samples will be collected for determination of levels of GSH cycle markers. A contract laboratory will receive samples via courier in order to test GSH cycle components and to perform the pharmacokinetic analysis. Additional information about the collection, handling, storage, and shipment of the GSH cycle marker samples will be provided separately prior to start of the study.

Blood samples for clinical laboratory measurements should be collected and processed according to the site's laboratory's standard procedure.

F. Efficacy Evaluations

F1. Glutathione Cycle Biomarkers

Plasma levels of oxidized and reduced GSH as well as GSH metabolites will be used to evaluate EPI-589 target engagement and ability to correct a key biochemical aspect of disease pathology.

F2. Neuroradiology

MRS will be used to measure GSH and other metabolites in the basal ganglia. Extent of cortical and basal degeneration will be assessed by MRI. Dopamine uptake will be measured by DaTscan.

F3. Parkinson's Disease Rating (MDS-UPDRS)

The MDS-UPDRS is a tool for monitoring the impact of PD, the degree of disability caused, and complications from treatment. Part I evaluates nonmotor experiences of daily living; Part II evaluates motor experiences of daily living; Part III is a motor examination and includes the Hoehn and Yahr scale; Part IV examines motor complications (e.g., motor fluctuations and dyskinesias).

Several questions from Part I and all questions from Part II are designed to be amenable to a patient/caregiver questionnaire format; the remaining interview (Part I and Part III) and examination (Part IV) are designed with the expectation they can be completed within 30 minutes. Each item is measured on a five-point scale.

F4. Non-motor Symptoms (NMSS)

Non-motor symptoms are evaluated using the NMSS which is divided into 30 questions in 9 different domains including such symptoms as dribbling saliva, constipation, depression, sleep disorders, apathy, hallucinations and dementia. Symptoms are quantified based on their severity (using a scale of 0 to 3) and frequency (using a scale of 0 to 4). The final cumulative scores are derived from adding up the product of the frequency score times severity score for each of the 30 questions.

F5. Parkinson's Disease Questionnaire (PDQ-39)

PDQ-39 is a self-administered questionnaire for patients with PD that has 39 questions relating to eight key areas of health and daily activities, including both motor and non-motor symptoms. It is scored on a scale of 0 to 100, with lower scores indicating better health, and high scores more severe symptoms.

F6. EQ-5D

EQ-5D is a questionnaire designed to provide measures of health-related quality of life states, consisting in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

F7. Montreal Cognitive Assessment (MoCA)

MoCA is a 30-point questionnaire for cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-

constructional skills, conceptual thinking, calculations, and orientation. Severity ranges are approximately: 26 to 30 normal; 18 to 26 mild cognitive impairment; 10-17 moderate cognitive impairment; < 10 severe cognitive impairment.

F8. Mattis Dementia Rating Scale (DRS-2)

The DRS-2 is an instrument used in screening for dementia designed for adults with cognitive impairment aged 56 and older. It provides a composite score and five subscale scores in Attention, Initiation-Perseveration, Construction, Conceptualization, and Memory.

F9. Beck Depression Inventory (BDI)

The BDI is a self-reporting inventory that measures characteristic attitudes and symptoms of depression, including physical symptoms. Twenty-one questions have four responses each (rated 0 to 3) with a total cumulative score scale ranging from 1-10 considered normal) > 40 (extreme depression).

F10. Montgomery and Asberg Depression rating scale (MADRS)

The MADRS is a clinician-rated tool for measuring changes in depressive symptom severity. Ten core symptoms and cognitive features are rated on a severity scale of 0 to 6. Higher scores indicate increasing depressive symptoms.

F11. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)

Timed motor tests are simple, objective, quantitative measures for the assessment of Parkinson's disease. They include, in an on-medication and an off-medication state, timed recorded physical movements.

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VII. STATISTICAL CONSIDERATIONS

A. Statistical Analysis

In this a within-subject, controlled open-label study changes from baseline to Month 3 will be calculated for each subject.

A1. Analysis Populations

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

B. Efficacy Analysis

B1. Primary Efficacy Variables

The primary efficacy variable is GSH cycle biomarkers (at baseline, Day 29 and Day 85).

B2. Secondary Endpoints

1. Brain MRS, DaTscan
2. MDS-UPDRS
3. NMSS
4. PDQ-39
5. EQ-5D
6. MoCA
7. DRS-2
8. BDI
9. MADRS
10. Timed motor tests in ON and OFF state (for subjects on dopamine therapy)

C. Safety Analysis

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 40 subjects (20 with genetically-defined subtypes of PD and 20 PD drug-naïve subjects).

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VIII. STUDY MEDICATION

A. Description

EPI-589 is presented as an immediate release film-coated tablet. Each tablet contains 250 mg of EPI-589 and the following compendial excipients: lactose, 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, in compliance 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 HPDE 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]).

C. 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 verification with subject-completed diary cards and returned used drug supply.

D. Drug Accountability

Dosing information will be captured on a subject Dosing Diary Form. This form is part of the 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 Investigator study file to assure the study medication is 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 either be 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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IX. 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 in accordance with the IRB policies and as detailed below. AEs that are not serious will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

B1. Safety Guidance

Based on the known clinical manifestations of Parkinson's disease, we expect that many AEs could occur during the course of the trial that are well documented to occur as the results of the natural history of this disease. These include, but are not limited to worsening neuromuscular function, depression, decline in cognitive function, loss of vision and other ophthalmological symptoms, loss of coordination and loss of speech.

Edison Pharmaceuticals 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, Edison Pharmaceuticals should be provided with a copy of any post-mortem findings, including histopathology.

C. Definition of an Adverse Event

C1. Adverse Event

An 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” or “AE”.

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)

An 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; or
5. A congenital anomaly/birth defect.

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 subject 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 an SAE which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether other AEs, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject, require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

[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, all pregnancies should be reported using the same process as for SAEs. Any pregnancy complications or an outcome other than a healthy, normal outcome will be recorded as an AE or SAE.

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.

C3. Non-serious Adverse Event

A non-serious AE 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 and reappears with re-introduction 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 indicated.

Grade 2 – Moderate limitation in activity, some assistance may be needed; minimal noninvasive medical intervention/therapy indicated.

Grade 3 – Severe limitation in activity, assistance usually required; medical intervention/therapy required; hospitalization or prolongation of hospitalization indicated; disabling.

Grade 4 – Extreme limitation in activity, significant assistance required; urgent medical intervention/therapy required; life-threatening consequences.

Grade 5 – Death

C6. Definition of Unexpected Adverse Event

Any AE, the specificity or severity of which is not consistent with those listed in the current investigator's brochure is considered "unexpected."

C7. Notification of SAEs

The Investigator is responsible for promptly notifying the IRB/IEC of all study on-site SAEs 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 MedWatch or CIOMs form (as appropriate).

SAEs (whether unexpected or expected AEs) must be documented on the designated SAE form. The SAE must be reported to the medical expert and appropriate Edison or Edison-assigned pharmacovigilance staff within 24 hours, according to regulatory, Sponsor, or ICH-E6 Good Clinical Practice, followed by the SAE form within two 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 Investigator and/or Medical Expert must also inform the Study Monitor and the Sponsor in all cases. Any SAEs must also be reported to the IRB/IEC. The Sponsor or designee will ensure that all legal reporting requirements are met.

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 a follow-up SAE forms.

The instructions to sites for the completion of SAE reports give detailed guidance on the reporting of SAEs and AEs initially reported as non-serious that become serious. When a non-serious event becomes serious, details must be forwarded immediately to the Medical expert and Edison or Edison-assigned 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 reported to the relevant competent authorities.

In the US, all fatal or life-threatening suspected unexpected serious adverse events assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA as soon as possible (i.e., by telephone or facsimile transmission), but no later than 7 calendar days after first knowledge by the Sponsor that a report qualifies as a suspected unexpected fatal or life-threatening reaction. All unexpected serious adverse events, other than fatal or life-threatening, assessed as possibly or probably related to study drug by the Sponsor must be reported to the FDA within 15 calendar days from the day the Sponsor determines that the information qualifies as a SUSAR.

In the UK, the Sponsor or trial investigator must act immediately or at least within 24 hours after becoming aware of a SUSAR by informing the MHRA's Clinical Trial Unit by telephone. The MHRA must then be informed in writing within 3 days of the incident. All SUSARs originating in the UK or originating outside the UK involving the same medicinal product are to be reported. Fatal or life-threatening SUSARs are to be reported as soon as possible, but no later than after 7 days. Any additional relevant information must be sent within 8 days of the report. Non-fatal or non-life-threatening SUSARs are to be reported as soon as possible but no later than 15 days after becoming aware of the reaction.

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. All SAEs should be followed until either resolved or stable.

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 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.

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X. 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 Edison 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 Edison. 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 Edison 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 (0.001%), a systematic review of the database will be undertaken and corrections will be made to achieve an error rate of less than 0.001%.

AEs will be coded using MedDRA, version (14.3). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary, March 2014.

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 or 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, and the General Data Protection Regulation (GDPR).

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 EPI-589-14-01 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 PD. Therefore, we cannot assure that subjects will benefit from treatment with EPI-589. Potential benefits may manifest in a variety of ways, such as in disease-related parameters, functioning, and quality of life.

G3. Risk-Benefit Assessment

There are no effective and/or approved disease modifying treatments available for PD, 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 hold benefit for patients with PD. This is the first study to better understand EPI-589 target engagement and potential therapeutic benefit in subjects with PD. 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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XI. PUBLICATION

A. Use of Study Results

All information concerning the product, as well as any matter concerning the operation of Edison (such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by Edison and are unpublished), are confidential and must remain the sole property of Edison. 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 Edison 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 Edison. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

This Study is part of a multicenter clinical research study. Accordingly, 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 while this Study is being conducted at other center/s. Only after the completion of this Study at all other centers, provision of the data to the FDA or EMA for review and comment, and publishing the combined data from all of the centers, may the Principal Investigator 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).

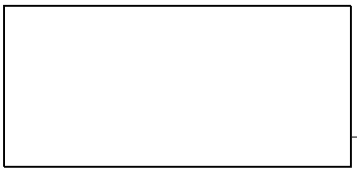
Without limiting the foregoing, Institution and Principal Investigator, and all other study investigators in other study institutions, shall give due regard to Sponsor’s legitimate interests, such as manuscript authorship, coordinating and maintaining the proprietary nature of submissions to health authorities, 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 Edison, Edison will allow the Investigator or CRO 60 days for full review of the manuscript before publication.

XII. LIST OF ABBREVIATIONS

AE	adverse event
AI	accumulation index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AR	accumulation ratio
BDI	Beck Depression Inventory
BID	twice daily
BSO	L-buthionine-(S,R)-sulfoximine
CBC	complete blood count
CFR	Code of Federal Regulations
CK	creatinine kinase
CNS	central nervous system
CoQ10	Coenzyme Q 10
CRF	Case Report Form
CRO	Contract Research Organization
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DaT	dopamine transporters
DSMB	data safety monitoring board
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EITT	efficacy intent-to-treat
EPDA	European Parkinson's Disease Association
EU	European Union
%F	percent fluctuation
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GCRC	good clinical research practice
GDPR	General Data Protection Regulation
GSH	glutathione
GSSG	glutathione disulfide
HDPE	high density polyethylene
hERG	human Ether-a-go-go Related Gene
HCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HMPAO	hexamethylpropylene amine oxime
ICF	informed consent form
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
λz	apparent terminal constant

LFT	liver function test
MAD	multiple ascending (oral) dose
MADRS	Montgomery and Asberg Depression rating scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
mg	milligram
mL	milliliter
MoCA	Montreal Cognitive Assessment
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPV	mean platelet volume
MRS	magnetic resonance spectroscopy
mtDNA	mitochondrial DNA
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NF	National Formulary
nM	nanomolar
NMSS	Non-motor Symptoms Scale
NOAEL	no observed adverse effect level
NQ01	NAD(P)H Quinone oxidoreductase 1
OD	once daily
OTC	over-the-counter
PD	Parkinson’s disease
PDQ-39	39-Item Parkinson’s Disease Questionnaire
PO	by mouth
PT	Prothrombin Time
PTT	Partial Prothrombin 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
SAD	single ascending (oral) dose
SAE	serious adverse event
SD	standard deviation
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



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