Title:	A Multicenter, Double-Blind, Parallel Group, Placebo Controlled Study of Creatine in Subjects with Treated Parkinson's Disease (PD). Long-term Study – 1 (LS-1)
Acronym:	NET-PD Long-term Study -1 (LS- 1)
Protocol No.:	NS43128 (NET-PD)
Clinical Phase:	Phase III
IND Number:	75,204
Sponsor:	NIH National Institute of Neurological Disorders and Stroke (NINDS) Building 31, 8A52 9000 Rockville Pike, Bethesda, Maryland 20892

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PROTOCOL (NET-PD LS-1)
INCLUDING AMENDMENT #7

A Multicenter, Double-Blind, Parallel Group, Placebo Controlled Study of Creatine in Subjects with Treated Parkinson's Disease (PD) – Phase III Long-term Study – 1

Karl Kieburtz, M.D., MPH
Principal Investigator, Coordination Center

2 Jul 12
Date

Barbara Tilley, PhD
Principal Investigator, Statistics Center

7/3/12
Date

Debra Babcock, M.D., PhD
Program Director, Clinical Trials, NINDS

7-3-12
Date

INVESTIGATOR AGREEMENT

I have carefully read this protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current Good Clinical Practice (GCP) regulations and guidelines, and local regulatory requirements. Any changes in procedure will only be made if necessary to eliminate immediate hazards and/or to protect the safety, rights or welfare of subjects.

I will provide copies of the protocol and all other information relating to the pre-clinical and prior clinical experience, which were furnished to me, to all physicians and other study personnel responsible to me who participate in this study. I will discuss this information with them to assure that they are adequately informed regarding the study drug and conduct of the study.

I will ensure that the drugs supplied to me for this study will be used only for administration to subjects enrolled in this study protocol and for no other purpose.

I agree to keep records on all subject information (case report forms, informed consent statements, drug shipment, drug return forms, and all other information collected during the study) in accordance with the current GCP, local and national regulations.

Print Site Investigator Name: _____

Site Number:_____ **Print Site Name:**_____

Address of Study Site: _____

_____

Telephone Number: _____

_____ _____

Site Investigator Signature **Date**

Summary of Changes to Protocol NS43128 (NET-PD)

Amendment # 7

Section	Change
Table of Contents	Updated to include 9.3, updated page numbers
Entire document	Corrected the name of Schwab and England to Modified Schwab and England (the instrument itself was unchanged)
3.1	Addition of information re: identification of a proxy
4.1	Correction to visit window +/- 14 days
4.1.3- 4.1.10	Updated activities and removed reference to ECGs as these are no longer being done
4.1.9	Update to label 99 changed to FNL; Final visit activities updated
4.1.12	Updated to Telephone visit
4.1.13	Addition of End of Study Visit
4.1.14	Re-Entry after premature withdrawal
5.1	Updated to End of Study EOS
5.2.3	Updated who receives reports and updated the eGFR follow up for those who alert before Month 60.
5.2.4	Update re: ECG assessments
5.2.5	Addition of Current Medical Conditions Log for subjects who return after premature withdrawal
5.3.1-5.3.6	Updated timing for completion of the instruments
5.3.9	Updated information about data sharing
9.1	Added regarding return to the study
9.3	Addition of section pertaining to subjects returning from premature withdrawal
9.3.1	Re-entry procedures
9.3.2	Study drug rechallenge guidance
11.6	Correction - removed “creatine result of” in first paragraph
17.1	Updated contact information for CTCC
17.2	Update on Independent Medical Monitor responsibilities
17.3.3	Updated frequency of OSB meetings
Appendix B	Updated Stats Center address
Appendix C	Updated SOA
Appendix D	Updated list of abbreviations
Appendix E	Updated Form

TABLE OF CONTENTS

1.0 OVERVIEW

There is extensive evidence of both oxidative stress and mitochondrial dysfunction in the pathogenesis of PD. Creatine could potentially support and stabilize mitochondrial function and act as an antioxidant. There is evidence of impaired function of complex I of the mitochondria in patients with PD which could result in reduced ATP synthesis and a bioenergetic deficiency. Furthermore, a complex I defect could lead to increased free radical production, and could promote signaling pathways that lead to apoptosis [Olanow, et al., 2002]. Creatine is converted to phosphocreatine, which in turn can transfer a phosphoryl group to ADP to make ATP, thereby buffering intracellular energy stores. It also may act as an indirect antioxidant by enhancing energy transduction. Creatine stabilizes mitochondrial creatine kinase, which in turn inhibits opening of the mitochondrial transition pore, a potential trigger of apoptosis [Tarnopolsky, et al., 2001; O'Gorman, 1997].

This will be a multi-center, double-blind, study to determine if creatine is more effective than placebo in slowing the clinical decline in PD patients with early, treated PD. Treated will be defined as receiving dopaminergic therapy (dopamine agonists or levodopa) for a period of greater than 90 days but not longer than 2 years. At least 1,720 subjects from approximately 50 sites in the U.S. and Canada will be enrolled. Subjects will be randomized in a 1:1 ratio to receive creatine or placebo. Subjects will remain on blinded study drug for a minimum of 5 years and until the last subject enrolled completes 5 years. The duration of the study is to be a minimum of 5 years in order to allow sufficient time to determine if the two groups differ in disease progression while continued follow up beyond 5 years will provide longer term information on progression for a subset of subjects.

1.1 PRIMARY SPECIFIC AIM

The primary study aim of this trial is to compare the primary outcome as measured by the Modified Schwab and England ADL (PD functioning) [Schwab et. al., 1969], PDQ-39 (QOL) [Bushnell et. al., 1999], ambulatory capacity (sum of 5 UPDRS questions: falling, freezing, walking, gait, postural stability), Symbol Digit Modalities (cognitive impairment) [Smith, 1973], and Modified Rankin value (global functioning) [van Swieten et. al., 1988] in the creatine group versus the placebo group against a background of dopaminergic therapy and best PD care.

The research hypothesis is that the group being treated with creatine will show less disease progression by 5 years than the group on placebo as evaluated by a Global Statistical Test comprised of the above measures.

1.2 SECONDARY SPECIFIC AIMS

Secondary specific aims are to compare the creatine and placebo groups on additional measures of efficacy, safety, and tolerability using data between baseline and 5 years follow up.

The hypotheses being tested are that the creatine group shows greater efficacy and similar safety and tolerability to placebo as measured by:

Efficacy:
UPDRS Parts I-IV [Goetz et al., 1995; Martinez Martin et al., 1994; Richards et al., 1994; Siderowf et al., 2002; Van Hilten et al., 1994]
Beck Depression Inventory II [Beck, 1996]
Total Functional Capacity (TFC) [Shoulson, 1989]
SCOPA-COG (Marinus, 2003)
Total Health Services Utilization over 5 years
EuroQOL (EQ-5D) [Gold et al, 1996]
Final dose of dopaminergic therapy at 5 years

Safety:
Serious Adverse Experiences (frequency, severity, hospitalizations)
Change in Vital Signs
Clinical Laboratories
Mortality

Tolerability:
Number of subjects who permanently discontinue the study treatment
Number of subjects who discontinue the study treatment due to adverse experiences
Number of subjects who decrease dosage of study treatment due to adverse experiences
Dose of study drug at the conclusion of the study

2.0 BACKGROUND AND RATIONALE

A major goal of the neuroscience community is to develop treatments that will slow or forestall the progression of Parkinson's disease (PD). PD is one of the most common adult-onset neurodegenerative disorders, affecting approximately 1 million people in North America and is characterized clinically by resting tremor, cogwheel rigidity, bradykinesia and postural instability [Lang & Lozano, 1998]. The clinical features of PD usually emerge in mid to late adulthood with tremor and bradykinesia being the most obvious initial manifestations. Illness and disability progressively advance despite treatments that temporarily ameliorate the signs and symptoms of PD. In the later stages of the illness approximately 75 percent of patients will develop deterioration in cognitive performance [Aarsland 2003; Hely 2005] and disorders of mood and behavior in addition to the progressive impairment of motor function. Eventually PD may lead to profound functional disability in the areas of employability, ambulation and self-care.

Although the advent of levodopa therapy has been associated with a prolongation of survival in PD, there is still substantial cognitive and functional disability associated with advancing PD [Hoehn, et al. 1967; Uitti, et al. 1993; Diamond, et al., 1987; Rajput, et al., 1984; Clarke, et al., 1995]. While current dopaminergic therapies in PD are symptomatic (relieve signs and symptoms), their long-term use is associated with the development of motor complications including fluctuations and dyskinesias. Moreover, no treatment has been definitively identified to slow the progression of PD, and it remains of interest to identify disease modifying agents.

The pathology of PD is characterized by the loss of pigmented neurons in the brainstem, particularly dopaminergic neurons in the substantia nigra pars compacta and noradrenergic neurons in the locus ceruleus as well as cortical neuronal loss. The loss of neurons is associated with the presence of intracytoplasmic eosinophilic inclusions (Lewy bodies) which contain both alpha-synuclein and ubiquitin. The cause of neuronal dysfunction and death, and the role of the intracytoplasmic inclusions remain unknown. These neuropathologic changes are associated with neurochemical abnormalities including diminished striatal levels of dopamine and its metabolites.

Although the pathogenesis of PD has not been fully elucidated, there is evidence that both genetic and environmental factors are involved. While for the majority of cases of PD there is no known genetic defect, several mutations cause parkinsonism including point mutations in the alpha-synuclein gene [Polymeropoulos, et al., 1997 and Kruger, 1998], *parkin* [Kitada, et al., 1998], *PINK1* [Valente EM, 2004], *DJ-1* [Bonifati V, 2003], and *Leucine-rich repeat kinase 2 [LRRK2]* [Paisan-Ruiz C., 2004 and Zimprich A, 2004] as well as alpha-synuclein gene duplication [Ibanez P, 2004; Chartier-Harlin MC, 2004] and triplication [Singleton AB, 2003]. Further evidence for the role of genetic factors in the etiology of PD is suggested by the familial aggregation of PD in Iceland [Sveinbjornsdottir, et al., 2000]. In addition, there are epidemiologic studies [Gorell, et al., 1998; Seidler, et al., 1996] suggesting that environmental factors may contribute to the development of PD. Currently, the relative contribution and importance of these factors are unknown.

Based on accumulated observations in animal models, there appear to be several classes of agents that may be useful as neuroprotective strategies. These classes include NOS inhibitors; anti-apoptotic agents such as JNK inhibitors; MAO-B inhibitors (via the mechanism of bcl-2 upregulation); neuroimmunophilin compounds; glutamate antagonists, including amantadine and riluzole; D_2 receptor agonists, including pramipexole; antioxidant agents, including creatine, Coenzyme Q_{10} and acetyl-levo-carnitine; and anti-inflammatory agents including sodium salicylate, acetylsalicylic acid and cyclo-oxygenase 2 inhibitors. In addition to having demonstrated efficacy in preclinical models of PD, several of these compounds have been tested in humans in dose ranging tolerability studies. The impact of MAO-B inhibitors on disease progression has also been reported [Parkinson Study Group, 1989 & 2002].

There is evidence of mitochondrial dysfunction in PD, with deficits in complex I activity in platelets of early PD patients [Parker,1989; Krige, 1992] and in post mortem substantia nigra pars compacta (SNpc) tissue of more advanced patients [Schapira, 1990]. Oral supplementation with creatine has been shown to protect against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced dopamine depletion in mice [Matthews, 1999; Klivenyi, 2003] and is protective in transgenic rodent models of HD [Andreassen, 2001; Ferrante, 2000] and ALS [Klivenyi, 1999; Zhang, 2003].

Creatine is a natural derivative of the amino acids arginine and glycine. In humans it is synthesized primarily in the liver, kidney and pancreas and can be supplied exogenously through the diet. The primary food sources are animal protein including meat and fish. Creatine plays an important role in mitochondrial energy production. Cells primarily use creatine in the intermediate form of phosphocreatine that serves as a phosphate donor to generate ATP from ADP. Creatine supplementation has generally been used by athletes for improving performance. Oral supplementation of creatine leads to increased plasma free creatine, increased muscle and brain creatine and phosphocreatine, and can lead to enhanced athletic performance [Williams, et al., 1998; Clark, 1998; Mujika, et al., 1997; Greenhaff, 1995; Balsom, et al., 1995; Kirksey, et al., 1997; Almada, et al., 1996; Earnest, et al., 1996; Tarnopolsky, et al., 1997; Andrews, et al., 1998; Gordon, et al., 1995; and Earnest, et al., 1995].

There have been no major safety or tolerability problems with oral supplementation of creatine in dosages as high as 20 gm per day for short periods in normal healthy individuals [Persky A, 2001]. The rationale for using creatine to modify disease progression in PD is based on its potential to support and stabilize mitochondrial function by serving as an energy buffer. Evidence of mitochondrial dysfunction and oxidative stress has been shown in experimental models of PD and in tissue from PD patients. Creatine could support or augment mitochondrial function by acting as an energy buffer, by acting indirectly as an antioxidant, and by antagonizing mitochondrial permeability [Tarnopolsky, et al., 2001].

2.1 CLINICAL EXPERIENCE

Creatine is distributed throughout the body with 95% present in skeletal muscle and the remaining 5% in the brain, liver, kidney, and testes. The average diet contains 1 to 2gm of creatine per day [Persky, et al., 2001]. As a dietary supplement creatine is available in a solution or solid dosage form. Following oral administration, creatine circulates to the brain and it is transported into cells by a high affinity transmembrane transport process [Tarnopolsky, et al., 2001; Persky, et al., 2001].

Creatine is a small, positively charged amino acid, not a large, neutral amino acid. Creatine absorption across the jejunal plasma membranes has been shown to be both Na+ and Cl- dependent (CT1 transporter) and the LNAA transporter has never been shown to

be Cl- dependent. Moreover, the CT1 transporter introduces the creatine into the cell and is not involved in creatine absorption. Creatine absorption is paracellular (Tosco M et al, J Membrane Biol 2004;202:85-95; Orsenigo MN et al., J Membrane Biol 2005:207:183-195. Given these facts, it is unlikely that there will be significant competition for absorption between creatine and levodopa as levodopa intestinal absorption is typically at the large neutral amino acids (LNAA) transporter level.

In animals, oral supplementation (human equivalent 400 mg/kg/day) significantly increases (30-54%) brain creatine (creatine/phosphcreatine) after 4 weeks. There is continued rise in brain creatine concentrations for up to 8 weeks. There have been no well-performed pharmacokinetic studies examining creatine. Preliminary reports show that creatine (1-10 gm) has a Tmax of < 2 hours; however with higher dosages, the Tmax is delayed to > 3 hours [Persky, et al., 2001]. This increase may be due to delayed absorption with increasing dosage as creatine is primarily transported across the intestine by amino acid transporters. The extent of creatine's protein binding is not known. Creatine is eliminated renally at a rate similar to xylose, suggesting that its renal elimination is comparable to glomerular filtration rate (GFR). However in unsupplemented patients, most creatine is reabsorbed after renal excretion [Persky, et al., 2001]. Many other variables are found to increase creatine uptake, including exercise, catecholamines, and IGF-1 and insulin [Persky, et al., 2001]. Creatine crosses the blood brain barrier and oral supplementation appears to increase brain levels by approximately 10% in healthy human volunteers [Tarnopolsky, et al., 2001].

A recent study titled A Multicenter, Double-Blind, Futility Study of Minocycline and Creatine in Subjects with early Parkinson's Disease (PD), funded by the National Institute of Neurological Disorders and Stroke (NINDS) evaluated creatine and minocycline for futility as disease modifying agents in PD. The goal of this trial was to test whether these agents had the potential to alter the short-term course of early PD relative to a predetermined threshold for progression of PD. Agents found to be futile in comparison to the threshold would not be considered for further clinical testing. Agents that were not found to be futile would not automatically advance to phase III clinical trials, but would receive consideration for further testing based on the overall profile including safety, tolerability, and activity [Ravina, 2006; Tilley, 2006]. Using the pre-specified threshold as well as thresholds based on more current control data, creatine was not found to be futile and therefore should be considered for further study. Creatine was well tolerated and 90% of subjects continued creatine throughout the 12 months of the study. Five serious adverse events occurred in the creatine group (cardiomyopathy, coronary artery disease, fatal motorcycle accident, myocardial infarction, and spinal stenosis surgery). An independent medical monitor judged that none of these events were definitely or probably related to creatine. There were 7 instances of elevated serum creatinine in 6 subjects in the creatine group [Ravina, 2006]. By 18 months, there were 3 subjects in the creatine arm who prematurely withdrew from the study (malaise, death due to a motorcycle accident, lost to follow-up) and 4 subjects in the placebo arm who

prematurely withdrew from the study (colon cancer, depression, 2 subjects were lost to follow-up). Six subjects in the creatine arm and 4 subjects in the placebo arm discontinued treatment but remained in the study up to 18 months.

In addition, an open label pilot study completed in the UK, in subjects with gene positive Huntington's disease using doses of 10 gm/day showed that this dose of creatine was safe and well tolerated for a period of 12 and 24 months. However, no conclusion as to whether creatine stabilized symptoms could be made [Tabrizi, 2005].

Groeneveld and colleagues completed a 16 month trial in subjects with ALS receiving 10 grams of creatine for up to 16 months. Although they did not find a beneficial effect of creatine, creatine did not lead to serious adverse effects and did not induce renal dysfunction in subjects without a history of renal dysfunction [Groeneveld, 2004].

3.0 STUDY POPULATION

3.1 SUBJECT ACCRUAL

The study is expected to begin enrollment in the third quarter of 2006 and be completed in the second quarter 2014. At least 1,720 subjects from approximately 50 sites are to be enrolled in the study during the study period. Subject accrual is expected to average 2 subjects /site/month. Subject enrollment will end when the planned number of subjects is reached, unless the study is terminated early. The Site Investigator should discuss with the Coordination Center Project Manager any anticipated problems with recruitment or delays in study completion. It is anticipated that a multifaceted approach to recruitment will be necessary with subjects being drawn from site's clinical practice but also regionally. Concerted efforts to perform outreach to local geriatricians, primary care physicians and neurologists will be required to recruit this study population. The Coordination Center will make every effort to ensure that the planned accrual rate is maintained.

Subjects will be asked to identify a research proxy if concern arises about their continuing capacity to participate in the study and to maintain informed consent. Identification of the proxy will be clearly documented in source documents.

3.2 INCLUSION CRITERIA

Subjects meeting all of the following criteria will be considered:

1. Subject is willing and able to give informed consent and is willing to commit to long-term follow-up.
2. PD (asymmetric features including bradykinesia plus resting tremor and/or rigidity) within 5 years of diagnosis.

3. Treated/responsive to dopaminergic therapy (dopamine agonists or levodopa) for at least 90 days, but not longer than 2 years.

3.3 EXCLUSION CRITERIA

1. Use of creatine 14 days prior to baseline or during the study.
2. Participation in other drug studies or receipt of other investigational drugs within 30 days prior to baseline.
3. History of known hypersensitivity or intolerability to creatine.
4. In the investigator's opinion, any unstable or clinically significant condition that would impair the subjects' ability to comply with long-term study follow-up.
5. Other known or suspected cause of parkinsonism (e.g. metabolic, drug induced (See Section 6.3.1), etc.), or any significant features suggestive of a diagnosis of atypical parkinsonism.
6. eGFR (MDRD equation) of less than 50 mL/min/1.73m^2 at baseline (See section 4.1.3 for additional information.)

3.4 WARNINGS/PRECAUTIONS

Creatine is classified as a dietary supplement that has been used as a performance-enhancing agent for athletes. It is available commercially over the counter and appears to be well tolerated. It may occasionally cause weight gain, limb swelling, nausea, vomiting, and diarrhea.

There are no known drug interactions with creatine. Creatine is contraindicated in those with renal failure and renal disorders such as nephrotic syndrome [PDR Nutritional Supplement, 2001**].**

Subjects will be evaluated at all study visits for adverse events. Safety laboratories including blood chemistry and blood hematology will be performed during the scheduled in-person study visits.

Female subjects will be advised to use adequate birth control throughout the study as the effects of creatine on the fetus are unknown. Adequate birth control methods include surgical sterilization, a partner who has had a vasectomy, oral contraceptives, condom plus spermicidal cream/jelly, cervical cap plus spermicidal cream/jelly, diaphragm plus spermicidal cream/jelly, or intrauterine device (in place for at least 3 months) plus spermicidal cream/jelly. Abstinence is considered an acceptable contraceptive regimen. If a subject becomes pregnant during the study, it is important that they contact the study physician immediately. If a subject reports a pregnancy, study medication must be discontinued immediately. However, the subject should be encouraged to continue follow-up within the study. Study drug may resume after the subject has completed the pregnancy and is no longer breastfeeding.

4.0 STUDY PROCEDURES

4.1 SCHEDULE OF ACTIVITIES

Study procedures and assessments with their timing are summarized in Appendix C. Study visits should be conducted within the visit window schedule ± 14 days. **For NET-PD LS-1, it is more important that the visits be within the window than performed by the same investigator, as long as the rater has been GST certified.**

4.1.1 SUBJECT IDENTIFICATION (ID) NUMBER

A 5-digit Subject Identification (ID) number will be used to identify the subject on all study eCRFs and blood specimens. Sites will receive a series of consecutive subject ID's beginning with 10000. Each potentially eligible person who has been pre-screened or screened for study participation is assigned a Subject ID from this list in sequential order. This Subject ID will be recorded on all eCRFs with the exception of the Drug Accountability log.

4.1.2 CTCC UNIQUE IDENTIFICATION (ID) NUMBER

The CTCC Unique ID system was designed to track individual subjects across multiple studies conducted by the CTCC without storing any personally identifiable information. The CTCC Unique ID is **not** the same as any other study ID number. Subjects will be given a 9-digit CTCC Unique Identification Number at the Screening/Baseline visit, once the subject has signed the informed consent.

Obtaining a Unique ID entails using a protected system and an algorithm of nine data element inputs (last name at birth, first name at birth, gender at birth, day, month and year at birth, city and country at birth, and mother's maiden name). This produces an electronic "fingerprint". The system stores only the "fingerprint" and clears the individual's inputted data elements from memory. The subject is then assigned a 9-digit CTCC Unique ID Number that is associated with their electronic "fingerprint".

The CTCC Unique ID Number will be provided to the subject by the coordinator who will also record this number on the Demographics eCRF.

If a subject has participated in previous CTCC studies and already has an existing CTCC Unique ID Number, that number will be used for

this study. If a subject forgets his/her CTCC Unique ID Number, the coordinator can assist in obtaining the number again.

4.1.3 SCREENING/BASELINE (VISIT SB) (All activities required at this visit should be completed on the same day. This visit should not be split into two days.)

- Obtain Written Informed Consent including blood sampling for future use
- Demographics
- Review Inclusion/Exclusion Criteria
- Medical History
- Family History
- PD Features
- Vital Signs (including height)
- UPDRS I-IV
- Diagnostic Features
- Primary Diagnosis
- Modified Schwab and England
- Modified Rankin
- Total Functional Capacity
- PDQ-39
- EQ 5-D
- Symbol Digit Modalities
- SCOPA-COG
- Beck Depression Inventory
- Clinical Laboratories- Urine pregnancy testing is required for all women unless they are two years postmenopausal or surgically sterilized
- Health Services Utilization
- Concomitant Medications
- Randomization Call/Assign Subject Number
- Dispense Study Drug

The above activities should be documented in the Source Documentation, including obtaining informed consent.

If the lab values obtained at the screening/baseline visit fall within those noted in Exclusion Criteria 6, the subject must be notified to discontinue study drug immediately and must return to the site for a premature withdrawal visit. Subjects who are discontinued from the study due to baseline lab values are not eligible to continue in the study in follow-up

alone. Subjects who were enrolled prior to this new exclusion (effective date 9/16/08) will not be retroactively excluded from the study.

4.1.4 MONTH THREE FOLLOW-UP VISIT (VISIT 01)

- Vital Signs
- UPDRS I-IV
- Clinical Laboratories
- Consent/Withdrawal of Consent for Optional Procedures
- Adverse Experiences
- Concomitant Medications
- Study Medication Adherence
- Dose Management
- Study Drug Accountability*

* Medication accountability will be completed and entered on the source document but not entered into the data base during this visit.

4.1.5 MONTH SIX and MONTH 18 FOLLOW-UP VISITS (VISIT 02, VISIT 04)

- Clinical Laboratories
- Consent/Withdrawal of Consent for Optional Procedures
- Health Services Utilization Questionnaire
- Supplemental Beverage Questionnaire**
- Adverse Experiences
- Concomitant Medications
- Study Medication Adherence
- Dose Management
- Dispense Study Drug
- Study Drug Accountability

** Supplemental Beverage Questionnaire completed only at Visit 4, Month 18

4.1.6 ANNUAL FOLLOW-UP VISITS - VISIT 03 (MONTH 12), VISIT 05 (MONTH 24), VISIT 06 (MONTH 36), VISIT 07 (MONTH 48)**

- Vital Signs
- UPDRS I-IV
- Modified Schwab and England
- Modified Rankin
- PDQ-39

- EQ-5D
- Symbol Digit Modalities Test
- Clinical Laboratories
- Consent/Withdrawal of Consent for Optional Procedures
- Health Services Utilization Questionnaire[+]
- Adverse Experiences
- Concomitant Medications
- Study Medication Adherence
- Dose Management
- Study Drug Accountability
- Dispense Study Drug

** These visits will continue on the same schedule until the end of the trial when all subjects (excepting those who have withdrawn) have at least 5 years follow up.

[+] After completion of the 60 month visit, the Health Services Utilization Questionnaire will no longer be required except during the End of Study or Premature Withdrawal visits.

All visits should be conducted in-person either inside or outside of the visit window. In lieu of a missed visit alternative arrangements i.e. phone visits may be employed to obtain data after discussion with the Project Manager.

4.1.7 ANNUAL PHONE VISITS - VISIT T01 (MONTH 30), VISIT T02 (MONTH 42), VISIT T03 (MONTH 54)**

- Health Services Utilization Questionnaire[+]
- Consent/Withdrawal of Consent for Optional Procedures
- Adverse Experiences
- Concomitant Medications
- Study Medication Adherence
- Dose Management
- Dispense Study Drug

** These visits will continue on the same schedule until the end of the trial when all subjects (except those who have withdrawn) have at least 5 years follow up.

[+] After completion of the 60 month visit, the Health Services Utilization Questionnaire will no longer be required except during the End of Study or Premature Withdrawal visits.

4.1.8 VISIT 8 (MONTH 60)

- Family History
- Vital Signs
- UPDRS I-IV
- Diagnostic Features
- Primary Diagnosis
- Modified Schwab and England
- Modified Rankin
- Total Functional Capacity
- PDQ-39
- EQ 5-D
- Symbol Digit Modalities
- SCOPA-COG
- Beck Depression Inventory
- Clinical Laboratories
- Consent/Withdrawal of Consent for Optional Procedures
- Health Services Utilization Questionnaire
- Adverse Experiences
- Concomitant Medications
- Study Medication Adherence
- Dose Management
- Study Drug Accountability
- Dispense Study Drug

4.1.9 FINAL STUDY VISIT (VISIT FNL)

The final study visit will occur at the End of Study Visit when all subjects have had at least 5 years follow-up or when a subject completes a Premature Withdrawal visit.

- Subject Conclusion
- OTC Creatine Use
- AE Follow up Log

4.1.10 PREMATURE WITHDRAWAL (PW)

Subjects may choose to withdraw from the study without prejudice. A premature withdrawal only occurs when a subject is no longer willing to provide consent to participate or is found to be ineligible based on baseline laboratory values. Subjects who withdraw from study drug, but who are willing to continue to be evaluated will NOT be considered prematurely withdrawn. (See Section 7.4)

Subjects withdrawing from the study will be asked to consent to one final phone contact by the site, at a time point coinciding with what would have been their expected study completion date, approximately 5 years after they originally enrolled in the study. (See section 4.1.12)

The Coordination Center must be informed within 24 hours of all study subjects who prematurely and permanently withdraw from the study.

Subjects who will not continue with any further visits should have a Premature Withdrawal visit completed which includes:

- Family History
- Vital Signs
- UPDRS I-IV
- Diagnostic Features
- Primary Diagnosis
- Modified Schwab and England
- Modified Rankin
- Total Functional Capacity
- PDQ-39
- EQ 5-D
- Symbol digit Modalities
- SCOPA-COG
- Beck Depression Inventory
- Clinical Laboratories
- Consent/Withdrawal of Consent for Optional Procedures
- Health Services Utilization Questionnaire
- Adverse Experiences
- Concomitant Medications
- Study Medication Adherence
- Dose Management
- Study Drug Accountability

All unused study drug should be returned to the investigative site during this visit.

4.1.11 UNSCHEDULED VISIT (U01, U02, etc.)

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the site Investigator. The date and reason for the unscheduled visit will be recorded in the subject's source documentation.

Unscheduled Visit Procedures & Evaluations:

In most cases an unscheduled visit will be due to an adverse event or a significantly abnormal lab value that needs to be reevaluated.

- Vital Signs
- Clinical Laboratories*
- Consent/Withdrawal of Consent for Optional Procedures
- Adverse Experiences
- Concomitant Medications
- Dose Management

* As necessary

4.1.12 FINAL TELEPHONE CONTACT AFTER WITHDRAWAL

As a key aim of this study is to gather data on progression of disease over a period of at least 5 years, subjects no longer wishing to participate in the study, either on study drug or in follow-up alone, will be offered an addendum consent which would allow the site to contact them at what would have been their projected study completion date (5 years after enrollment). Subjects consenting to this will be contacted by phone to ask about changes in their medical condition and the current status of Parkinson's symptoms. This information will be added to the study record.

The following assessments should be conducted via this phone contact, as agreed to by the subject. **Assessments should be conducted in the following order:**

- Modified Schwab and England
- Modified Rankin Scale
- PDQ 39
- EuroQual-5D
- Total Functional Capacity

4.1.13 END OF STUDY VISIT (EOS)

Subjects completing their last in-person study visit between June 2014 and May 2015 should complete the EOS in lieu of the annual in-person visit.

- Family History
- Vital Signs
- UPDRS I-IV

- Diagnostic Features
- Primary Diagnosis
- Modified Schwab and England
- Modified Rankin
- Total Functional Capacity
- PDQ-39
- EQ 5-D
- Symbol Digit Modalities
- SCOPA-COG
- Beck Depression Inventory
- Clinical Laboratories
- Consent/Withdrawal of Consent for Optional Procedures
- Health Services Utilization Questionnaire
- Adverse Experiences
- Concomitant Medications
- Study Medication Adherence
- Dose Management
- Study Drug Accountability

4.1.14 RE-ENTRY AFTER PREMATURE WITHDRAWAL

Subject retention is important to the validity of the study and therefore subjects who have withdrawn (by virtue of being lost to follow up or who have withdrawn consent) from the study are encouraged to return if they so choose and their current health status permits. A single certified letter will be sent to subjects who have previously withdrawn which details the option to return to the study. The subject must respond to the letter by contacting the site personnel in order to re-enter the study.

The Coordination Center must be informed within 24 hours of all study subjects who wish to return to the study after premature withdrawal.

Re-entry into the study may occur only when the subject notifies study staff of their interest in returning to the study. Subjects must be re-consented. Following re-consent subjects will either complete a recent (<3 month) missed in-person visit or return for an unscheduled visit using the current Schedule of Activities. In addition to the visit or unscheduled visit the following are REQUIRED activities:

- Written re-consent
- Clinical laboratories
- Current Medical Conditions Log

The subject will then return to the originally scheduled visits identified during randomization**.**

Upon review of the clinical laboratories and current health status, if the subject is deemed eligible and is willing to rechallenge with study drug, the site must notify the CTCC to activate drug supply for the subject (see Section 9.3 re: rechallenge of study drug.)

5.0 INSTRUMENTS FOR ASSESSING OUTCOMES

5.1 PRIMARY OUTCOME MEASURES

The assessments will be obtained at Screening/Baseline and during all annual visits and continue until the end of the trial when all subjects (except those who have prematurely withdrawn) have completed at least 5 years of participation. They will also be completed during the End of Study Visit (EOS).

5.1.1 AMBULATORY CAPACITY

(5 questions from the UPDRS)

The Unified Parkinson's Disease Rating Scale (UPDRS) [Goetz et al., 1995; Martinez Martin et al., 1994; Richards et al., 1994; Siderowf et al., 2002; Van Hilten et al., 1994] is a widely used and well-studied clinical rating scale for assessing the progression of disability in PD. For the primary analysis the five questions related to gait (question 29), freezing (question 14), walking (question 15), falls (question 13), and postural stability (question 30) will be summed and included as one measure in the Global Statistical Test.

5.1.2 MODIFIED RANKIN SCALE

The Modified Rankin Scale [van Swieten et. al., 1988] is widely used as a functional outcome measure in stroke and has been validated [Burn, 1992; Sulter et. al., 1999; Wilson et. al., 2002; Wilson et. al., 2005; Shinohara et. al., 2006]. The Modified Rankin measures levels of disability.

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5.1.3 MODIFIED SCHWAB AND ENGLAND SCALE

The Modified Schwab and England scale [Fahn, 1987, Schwab et. al., 1969; McRae, 2000] is an Investigator assessment of the subject's level of independence. The subject will be scored on a percentage scale reflective of his/her ability to perform acts of daily living in relation to what he/she did before Parkinson's disease appeared. Scores with associated descriptors range in increments of 10 with 100% for normal (subject has full ability and is completely independent; essentially

normal), to 0% (vegetative functions such as swallowing, bladder and bowel functions are not functioning; bedridden). The investigator may rate this scale using increments of 5% using a consensus rating based on historical information provided by the subject and/or others. **For subjects with motor fluctuations the Investigator will complete the Modified Schwab and England Scale in the "ON" and "OFF" state.**

5.1.4 PDQ-39

The PDQ-39 [Jenkinson et. al., 2003] is a self-administered disease-specific questionnaire that comprises 39 items addressing eight domains of health that patients consider to be adversely affected by the disease. This includes:
Mobility (e.g. fear of falling when walking)
Activities of daily living (e.g. difficulty cutting food)
Emotional well-being (e.g. feelings of isolation)
Stigma (e.g. social embarrassment)
Social support
Cognition
Communication
Bodily discomfort

The PDQ-39 is scored on a scale of 0 to 100, where lower scores indicate a better-perceived health status. Higher scores are consistently associated with the more severe symptoms of the disease such as tremor and stiffness. The results are presented as eight discrete domain scores as well as a summary score. The summary score will be included in the global statistical test. There is much literature on the reliability and validity of this scale [Jenkinson et. al., 2003,; Peto et. al., 1998; Marinus et. al., 2002].

At the discretion of the study personnel, this instrument may be mailed to subjects for completion at home and returned during required evaluations.

See Appendix E for a copy of the PDQ-39 scale.

5.1.5 SYMBOL DIGIT MODALITIES TEST

The Symbol Digit Modalities Test (SDMT) [Smith A, 1973] screens cognitive impairment by using a simple substitution task that adults and children with normal functioning can easily perform. Using a reference key, the examinee has 90 seconds to match specific numbers with geometric figures. Responses will be oral, allowing the test to be used with individuals with motor disabilities. The SDMT is relatively

culture free since it uses only geometric figures and numbers. Norms for adults are separated by age group and educational level. Literature suggests this is a robust neuropsychological screening tool and reliability has been examined [Sheridan, 2006; Hinon-Bayre, 2005].

5.2 SAFETY ASSESSMENTS

Adverse events, including frequency and severity, will be compared between the treatment groups. Changes in vital signs, clinical laboratories, rate of hospitalizations and mortality will be compared between the two treatment groups.

Tolerability will be evaluated between the treatment groups by comparing: number of subjects who permanently discontinue the study treatment, number of subjects who discontinue the study treatment due to AEs, number of subjects who decrease dosage of study treatment due to AEs, as well as the dosage of study drug at the conclusion of the study.

5.2.1 MEDICAL HISTORY

A medical history will be performed at the Screening/ Baseline visit.

5.2.2 VITAL SIGNS/WEIGHT/HEIGHT

Blood pressure (supine 1-3 minutes and standing after 1-3 minutes) and body weight (kg) changes felt to be a clinically significant change (worsening) when compared to Screening/ Baseline values should be considered an adverse event, recorded, and monitored as described in Section 10.3. Height will only be measured during the Screening/Baseline evaluation.

5.2.3 CLINICAL LABORATORY TESTS

Clinical laboratory tests will be performed by a central lab and the laboratory's reference ranges and alert values will be used. The Coordination Center must be notified during the study of any changes to the central lab reference ranges. All samples for laboratory analyses must be collected, prepared, labeled, and shipped according to the laboratory's requirements.

Blood samples and urinalysis will be collected at all scheduled in-person study visits for the standard clinical safety laboratory analyses noted below. Retests may be performed if needed between visits for abnormal results.

Clinical laboratory test results will be forwarded to individual Investigators (** except as noted below), the Coordination Center and the Clinical Monitor. Site Investigators will determine the clinical significance of abnormal laboratories. Clinically significant change (worsening) when compared to Baseline values

should be considered an adverse event, recorded, and monitored as described in Section 10.3.

Clinical Laboratory Tests:

Urinalysis- dipstick will be performed.

Pregnancy Tests – human chorionic gonadotrophin urine tests will be performed for women of childbearing potential before being randomized into the study. Subjects of child-bearing potential must use adequate birth control throughout the study. Any subject becoming pregnant during the study will be withdrawn from study drug but will be encouraged to continue to be followed in the study. All pregnancies that occur during the study are to be reported to the Coordination Center and followed to their conclusion. Study drug may resume after the subject has completed their pregnancy and is no longer breastfeeding.

Hematology – CBC and platelets

Clinical Chemistry – (albumin, Alk Phos, AST, ALT, Ca, CL, CO2, Creatinine**, eGFR, Glucose, K, Na, T. bili, TP, BUN, uric acid)

Evaluating a Subject's Renal Function or other abnormal lab value:

**The use of creatine, in some individuals, has been associated with an elevation in serum creatinine levels. There is no evidence that creatine causes renal insufficiency. In order to maintain the blind, creatinine will only be reported to the Site Investigator at the Screening/Baseline visit. Thereafter, the creatinine will be completed but redacted from the Investigator's laboratory report except as noted below.

Creatinine values after **9/16/08** which reach the upper alert limit of 2.0 mg/dL or values that double from baseline will be sent to the Site Investigator, the Clinical Monitor and the Coordination Center for follow up. In addition, an eGFR value of <30 will also be considered an alert limit. The Clinical Monitor and/or the Coordination Center will contact the site investigator as needed. The Coordination Center will notify the site that the subject's study drug must be permanently suspended immediately. The site will have the subject return for an unscheduled visit in 2-3 weeks to determine whether the creatinine level and/or eGFR has returned to baseline. Because the study is blinded, patients with elevated creatinine should be evaluated by their primary care physician in case there is another cause for the elevated creatinine or need for other treatment. The subject's primary care physician should be informed of the

elevated creatinine value and that follow-up laboratory testing will be scheduled in 2-3 weeks.

When the subject returns for the unscheduled visit, he/she is told that study medication is permanently suspended but that he is encouraged to continue in the study for safety follow-up. A full laboratory panel, including U/A, should be drawn and sent to the central lab.

If the eGFR at the first unscheduled visit has NOT returned to baseline level (within 10%) the subject should be called and strongly advised to make an appointment with his/her primary care physician (if not already done) for further follow-up of kidney function.

Further study follow-up visits should be conducted to obtain updated adverse events and full laboratory analyses on the subject every 3 months until the eGFR level: 1) for subjects who had an eGFR of greater than or equal to 60 at Baseline returns to an eGFR greater than or equal to 60 or 2) for subjects with an eGFR less than 60 at Baseline the level must return to within 10% of the Baseline value. Subsequently, subjects should be monitored in person or via telephone every 3 months for adverse events and have lab values repeated every 6 months until the Month 60 visit at which time follow up of the elevated creatinine and eGFR will be completed only during annual in-person visits when full laboratory analyses occur. At this point, the subject's Primary Care Physician (PCP) should be sent an update regarding the subject's overall status including laboratory findings. Additional follow up of abnormal laboratory findings should be at the discretion of the PCP. Subjects who have the first observance of elevated creatinine and eGFR at or after Month 60 will stop study drug as above and undergo follow up every 3 months until the eGFR level has returned to baseline as described above. Subsequently, subjects should be monitored in person or via telephone every 3 months for adverse events and have lab values repeated every 6 months.

Once a subject's creatinine level reaches the upper alert limit (2.0 mg/dL or doubles from baseline), the creatinine level will be reported on all future lab reports to enable the Clinical Monitor and Site Investigator to monitor the subject's return to baseline.

The Site Investigator must carefully monitor the subjects' renal status through review of the BUN and urinalysis. The clinical significance and subsequent evaluation of an elevation in BUN or any other lab value will be left to the judgment of the Site Investigator.

However, if at any time the Investigator believes ***any value*** to be a significant change from Baseline, study drug may be suspended and a repeat laboratory completed within 7 days. Study drug may remain suspended until the significant change resolves. (The frequency of repeat laboratory or any additional testing is at the discretion and medical judgment of the Site Investigator).

Upon resolution of the significant change (except the creatinine or eGFR), at the discretion of the Site Investigator, the subject may resume study drug using the rechallenge rules noted in Section 7.4. In the event that there is no resolution to the significant change, the subject will permanently suspend study medication but will be encouraged to continue follow-up in the study.

5.2.4 ECG ASSESSMENTS

12- Lead Electrocardiogram assessments will be performed on a subset of the cohort at Screening/Baseline, months 6, 12, 36 and 60. These will be performed at select sites and sent to a central laboratory for analysis and results will be sent to the CTCC database. Pending the analyses of the findings and their review, these assessments may either be discontinued or expanded to the entire cohort.

Update: ECG assessments were discontinued November 30, 2011 after approval by the FDA.

5.2.5 CURRENT MEDICAL CONDITIONS

Subjects who return to the study after a Premature Withdrawal will be asked to provide updated medical information. This will be capture on the Current Medical Conditions Log which is similar to the Medical History captured at the Screening/Baseline visit.

5.3 OTHER ASSESSMENTS

5.3.1 UPDRS PARTS I-IV

This widely used scale has four components; Parts I-III consist of questions answered on a 0-4 point scale [Fahn, 1987, Goetz et al., 1995; Martinez Martin et al., 1994; Richards et al., 1994; Siderowf et al., 2002; Van Hilten et al., 1994]. Part I assesses mentation, behavior and mood; Part II assesses activities of daily living in the week prior to the designated visit and Part III assesses motor abilities at the time of the visit. A total of 31 items are included in Parts I, II and III. Each item will receive a score ranging from 0 to 4 where 0 represents the absence of impairment and 4 represents the highest degree of impairment.

Part IV of this scale deals with the complications associated with Parkinson's disease therapy.

Subjects will be assessed by the Investigator or trained designee on Parts I, II, III and IV of the UPDRS at the Screening/Baseline, and 3, 12, 24, 36, 48*, 60 Month visits and at the End of Study or Premature Withdrawal visits. All enrolling Investigators and designees will receive training on how to complete the UPDRS to ensure standardization of the procedure.

*Completed at all in-person visits beyond Month 60.

5.3.2 SCOPA-COG

The SCOPA-COG [Marinus, 2003] is a practical instrument that is sensitive to the specific cognitive deficits in Parkinson's disease. It consists of 10 items with a maximum score of 43, the higher score reflecting better performance.

This instrument will be completed at the Baseline, Month 60 Visit and the End of Study or Premature Withdrawal visits.

5.3.3 BECK DEPRESSION INVENTORY II

The Beck Depression Inventory II (BDI) [Beck, 1996] is a widely used instrument for detecting depression and takes approximately five minutes to complete. The BDI has been validated for use in Parkinson's disease [Visser, 2006].

The inventory consists of 21 items to assess the intensity of depression. Each item is a list of four statements arranged in increasing severity about a particular symptom of depression.

This assessment will be obtained at Screening/Baseline, the Month 60 and the End of Study or Premature Withdrawal visits. At the discretion of the study personnel, this instrument may be mailed to subjects for completion at home and returned during required evaluations.

Subjects who endorse active suicidality (at any time) will be evaluated by the Site Investigator and referred for appropriate follow-up with their primary care physician and/or a psychiatric care provider if this is felt to be clinically indicated.

See Appendix F for a copy of the Beck Depression Inventory II.

5.3.4 TOTAL FUNCTIONAL CAPACITY

This brief scale [Shoulson, 1989] reviews a subject's potential for occupational capacity, financial abilities, ability to perform ADLs and domestic responsibilities and living situation.

This assessment will be obtained at Screening/ Baseline, Month 60 and the End of Study or Premature Withdrawal visits.

5.3.5 HEALTH SERVICES UTILIZATION

Health care utilization and costs between the treatment groups will be compared using the Health Care Utilization questionnaire, adverse event data on hospitalizations and emergency department use, and the concomitant medication data. These data will be combined with hospital billing data, and cost weights derived from several large medical billing data bases to construct the measures required to assess cost effectiveness and compare expected economic impacts for the therapy over time.

This assessment will be obtained at **all** visits up to 5 years (Month 60 visit), with the exception of Month 3 and Unscheduled Visits. This will also be completed during the End of Study or Premature Withdrawal visits. At the discretion of the study personnel, this instrument may be mailed to subjects for completion at home and returned during in-person evaluations or returned via mail to the study personnel when required at telephone visits.

See Appendix G for a copy of the Health Services Utilization Questionnaire.

5.3.6 EuroQOL-5D (EQ-5D)

The EuroQOL Group's EQ-5D is a brief, preference-based health status measure designed for use in evaluative studies and policy research, and has been recommended for use by the US Public Health Service's Panel on Cost-Effectiveness in Health and Medicine (EuroQOL Group, 1990; Gold et al, 1996; Dolan et al, 1995; Dolan, 1997). Prior studies have demonstrated the appropriateness of using the EQ-5D in Parkinson Disease patients (Dolan, 1997, Siderowf et al, 2002; Brazier et al, 1996).

This assessment will be obtained at Screening/Baseline and during all annual visits and continues until the end of the trial when all subjects (except those who have prematurely withdrawn) have completed at least 5 years of participation. It will also be completed during the End of

Study or Premature Withdrawal visits.. At the discretion of the study personnel, this instrument may be mailed to subjects for completion at home and returned during required evaluations.

See Appendix H for a copy of the EuroQOL EQ-5D.

5.3.7 SUPPLEMENTAL BEVERAGE QUESTIONNAIRE

The Supplemental Beverage questionnaire is a self administered instrument which estimates a subjects' caffeine consumption in coffee, tea and other caffeinated beverages.

See Appendix I for a copy of the Supplemental Beverage Questionnaire.

5.3.8 SAMPLING FOR THE NINDS REPOSITORY

Subjects may be asked to contribute a blood sample to the NINDS Human Genetics Resource Center at the Coriell Institute for Medical Research. The overall goal of the NINDS Resource Center is to establish a bank of samples from individuals with neurological diseases. This bank will allow for distribution of cell lines and DNA to scientists to help learn more about the genetic components of neurological diseases and many other diseases and genetic factors. Subjects will have the ability to "opt out" of this activity or have their sample withdrawn at any time should they later change their mind. Subjects who choose not to participate in the NINDS Repository sampling may still be part of the study. Samples may be collected at any visit throughout the study. Sampling of DNA will be dependent on continuation of funding to Coriell via NINDS. This will be reviewed on an annual basis and may be halted if funding is no longer available.

5.3.9 DATA SHARING

Government funded studies require data sharing. All subjects will be informed that the study team will share some of their research data. The data base is supported by the National Institutes of Health (NIH) to advance research by creating large, shared sets of information (data). The information we collect will be coded and added to other data contributed by individuals from across the country, and may be used to develop future studies of PD or other disorders. By using this code, the subject's identity will not be disclosed to any researchers using this data in the future.

5.4 ASSESSMENT OF SUBJECT COMPLIANCE

At each in-person study visit, the Investigator and/or Study Coordinator will assess the subject's compliance with the study requirements. This will include checks of protocol compliance, concomitant medication use, and use of study drug. The primary mechanism for assessing compliance with use of study drug will include completion of a Study Medication Adherence Questionnaire [Morisky, 1986]. In addition, sachet counts will be documented on the Drug Accountability Tracking Log (i.e., the number of sachets dispensed and returned at each visit will be documented).

6.0 CONCOMITANT MEDICATIONS

6.1 MEDICATION DATA COLLECTION

6.1.1 PRIOR MEDICATION THERAPY

Any prior or concomitant therapy or medication given to a subject 180 days prior to the Screening/ Baseline visit, or during study drug administration, will be indicated on the Concomitant Medication Log. If therapies outside the 180 days were used to determine eligibility these should be listed as well. Generic or trade name, and dosage will be indicated. All medications will be coded according to the MedDRA Drug dictionary.

At the Screening/Baseline visit, the Site Investigator or Coordinator will ask the subject about the current use of medications, including Over the Counter (OTC) medications, vitamins, and herbals

6.1.2 CONCOMITANT MEDICATIONS DURING THE STUDY

At each study visit (in-person or telephone) after randomization, the Investigator or Coordinator will inquire about use of medications since the previous visit, and will record any additions, deletions, and/or changes on the Concomitant Medication Log.

6.2 ALLOWED CONCOMITANT MEDICATIONS DURING THE STUDY

The subject may take any medication other than creatine as prescribed by their primary doctor, neurologist or other provider. Subjects should receive the best medical management for their PD symptoms throughout their participation without restriction after randomization.

6.3 DISALLOWED MEDICATIONS

6.3.1 DISALLOWED MEDICATIONS PRIOR TO STUDY ENTRY

Subjects who have used any of the following medications within 90 days of the Screening/Baseline evaluation will <u>not be eligible</u> for participation in this study:

- Methylphenidate
- Cinnarizine
- Reserpine
- Amphetamines
- MAO-A inhibitors

Subjects who have used any of the following medications within 180 days of the Screening/Baseline evaluation will not be eligible for participation in this study:

- Neuroleptics
- Metoclopramide
- Alpha-methyldopa
- Olanzapine
- Clozapine
- Flunarizine

6.3.2 DISALLOWED MEDICATIONS DURING THE STUDY

Subjects in this study must refrain from taking over the counter creatine for the duration of their study participation.

7.0 STUDY DRUG ADMINISTRATION/ASSIGNMENT

7.1 STUDY DRUG

Avicena Group, Inc. will supply active and placebo creatine packets**.** Supplies will be shipped to the Clinical Materials Services Unit (CMSU) of the University of Rochester. The CMSU will label and distribute the drug kits according to the randomization scheme and ship the drug to the sites. Sites will dispense study medication every 6 months to subjects participating in the study.

Study Drug Accountability, Storage and Security

The Site Investigator must ensure that all investigational drug supplies are kept in a locked, safe area under appropriate storage conditions with access limited to those directly involved in the study. Investigational drug supplies should not be repackaged in any way. The study drug should be stored at controlled room temperature 15°-30°C (59°-86°F).

The Site Investigator or Pharmacist (if applicable) must maintain accurate records of receipt of all drugs sent by the Clinical Materials Services Unit.

Drug accountability records must be filled out to account for the dispensing of the study drug. The site monitor will review accountability and compliance during monitoring visits. After accounting of the study product at the periodic monitoring visits, the site will be allowed to destroy unused study drug following their institutional guidelines. A copy of their institution's policy for destruction or a Note to File outlining the procedure will be kept in the site's files and a copy forwarded to the Coordination Center.

7.2 ENROLLMENT ID NUMBER ASSIGNMENT

Study drug will be pre-coded by the Clinical Materials Services Unit with Enrollment ID/kit numbers (based on the randomization plan generated by the Statistical Center). Pre-assigned start-up study drug kits will be supplied to the Site Investigator.

The treatment for each subject will be assigned by a randomized code. A stratified blocked randomization scheme (using a SAS® program) will be used to ensure approximate, even distribution of subjects into the two treatment groups at each participating site. Site will be the only stratifying variable. Block size will be randomly chosen.

The randomization algorithm and subject enrollment process will be implemented through the Internet accessible Electronic Data Capture (EDC) system using authenticated, password-protected accounts for each study site. The EDC system will automatically validate inclusion/exclusion criteria, and generate visit windows. Study medication re-supply will be coordinated through the Clinical Materials Services Unit.

All site personnel and Coordination Center staff will remain blinded as to treatment assignments until the conclusion of the entire study and after publication of the primary results. The treatment assignments are not part of the Coordination Center electronic database. A designated unblinded programmer and unblinded statistician in the Statistical Center will have access to the treatment assignments, and these individuals will not communicate about study-related matters to any other staff involved in the study.

7.3 CODING/EMERGENCY DRUG DISCLOSURE

The Clinical Materials Service Unit will distribute sealed emergency drug disclosure envelopes with individual treatment assignments which have been prepared by the Statistical Center. The Site Investigator or site Pharmacist (if applicable) will be provided with a sealed envelope containing a set of individual sealed envelopes, each containing the drug code for each subject. A sealed list of individual treatment codes will also be maintained in the Statistical Center. An individual subject's envelope should be opened only in

the rare case of a medical emergency when the site Investigator believes that discontinuation of the study medication is not sufficient and that treatment assignment must be known to ensure subject safety.

Premature discontinuation from the study medication, study dropouts, nor most clinical emergencies necessitate disclosure of treatment assignment. Most emergency situations can be handled by withdrawing study drug without disclosure of treatment assignment. However, in rare circumstances under which knowledge of the drug assignment is necessary for the treatment of a serious adverse event, site Investigators are encouraged to discuss the situation with the Coordination Center Clinical Monitor before deciding whether or not to disclose treatment assignment.

Disclosure of individual treatment assignment would be made by opening the disclosure envelope maintained at the site. Assigned drug treatment must not be revealed to any other study staff, Coordination Center staff or to individuals who are not involved directly in the clinical care of the subject unless disclosure to him/her is critical to the care of the subject**. Within 24 hours after disclosure of treatment assignment, the Investigator or Coordinator must call the Coordination Center to report the disclosure, and the subject will be permanently withdrawn from further exposure to study medication.**

If a drug disclosure is made, a record must be made by the site Investigator detailing the purpose, date and personnel involved. The disclosure card should then be placed in a sealed envelope and returned to the original envelope containing all of the disclosure cards.

All sealed and unsealed code envelopes will be returned to the Clinical Materials Service Unit at the conclusion of the study, where they will be inspected to ensure that they have not been opened.

7.4 DOSAGE OF STUDY DRUG

Subjects will be randomly assigned to receive one of the following regimens (1:1 ratio), which includes study drug (creatine) or placebo:

Creatine 10 gm/day (one 5 gm sachet BID) or
Matching placebo (one 5 gm sachet BID)

Theoretically, caffeine (in coffee, tea and caffeinated beverages) may interfere with the beneficial effects of creatine supplementation. [PDR Nutritional Supplement, 2001]. As this theory has not been substantiated, this study will not restrict dietary caffeine, however, subjects should be advised to avoid the

use of caffeine supplements or caffeine tablets at the same time study drug is taken [Vanakoski, 1998].

Titration Period (Screening/Baseline through day 3)
Each subject will take one dose of study drug at the Screening/ Baseline visit while in the clinic. The following two days subjects will continue to take only one dose of the study drug with the evening meal. A total of one 5 gm sachet of creatine or matching placebo will be taken at each dose mixed with 8 ounces of fruit juice or 4 ounces soft solids such as yogurt, applesauce or pudding.

Maintenance Period (Day 4 through Study completion)
Starting on day 4 of the study, subjects will take the study drug twice daily, with the morning and evening meals. A total of one 5 gm sachet of creatine or matching placebo will be taken at each dose mixed with 8 ounces of fruit juice or 4 ounces soft solids such as yogurt, applesauce or pudding daily. Subjects will be given enough supplies of study drug to last for a six month period. Study drug must be sent via courier at the Month 30, 42 and 54 visits. All subjects will receive study drug treatment for up to a minimum of 5 years or until the last subject has completed the study.

Dose Reductions: Dose reductions are permitted at any time during the study due to intolerable side effects that are thought to be related to study drug. The Investigator should be consulted prior to the subject reducing their dose of study drug. A dose reduction is accomplished by completely eliminating one dose of study drug. This dose reduction is a dose halving. Subjects who have had a dose reduction may at the discretion of the Investigator be rechallenged to a full dose of study drug. If the adverse event recurs as the dosage is increased, the subject should continue on the half dose.

Dose Suspensions: Administration of the study drug may also be interrupted for intolerable side effects thought to be related to study drug, if determined necessary by the Investigator.

Dose Rechallenge: Subjects who have had a dose reduction (a dose halving) may be rechallenged after the subject has tolerated a reduced dose for two or more full days (greater than or equal to 48 hours). The dose rechallenge is accomplished by adding back the missed dose.

For subjects that have had a dose suspension, the study drug rechallenge will be accomplished by taking only the evening dose for 2 full days and on the third day resuming full bid dosing (morning and evening). If full bid dosing is not tolerated the subject should return to the dose that was tolerated.

If the Investigator believes that the study drug should be temporarily or permanently suspended or dose halved due to intolerable side effects thought to be related to study drug, the subject should, if willing, continue to be followed within the study.

The Coordination Center must be informed within 24 hours of all study subjects who dose reduce, suspend, rechallenge or permanently discontinue the study drug. These subjects should be encouraged to remain in the study and complete all subsequent study visits.

All study drug modifications should be recorded.

8.0 INTERCURRENT ILLNESS

In the event of an intercurrent illness and at the discretion of the Investigator, the subject should be continued in the study with study drug treatment. The clinical course of the intercurrent illness will be followed to its appropriate conclusion and full notation made in the case report forms (eCRFs).

All intercurrent illnesses must be recorded in the eCRF as adverse events. Additional information may be required by the Coordination Center for serious adverse events.

9.0 SUBJECT DROPOUTS/RETENTION

9.1 DROPOUTS

Every attempt will be made to continue to gather the subject assessments, whether or not they can come for in-person visits or provide mail-in and phone data, provided appropriate consent is in place.

Should a subject withdraw from the study, i.e., refuse to have any further follow-up data of any kind collected after administration of the study drug, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A final evaluation at the time of the subject's withdrawal should be made and an explanation given of why the subject is withdrawing from the study.

The reason for and date of withdrawal must be recorded on the eCRF. If the reason for withdrawal is a clinical adverse event or a clinically significant abnormal laboratory test result, monitoring will continue until the event has resolved or stabilized. The specific event or test result(s) must be recorded on the eCRF. Final evaluations should be performed on the last day the subject takes the study drug, or as soon as possible thereafter.

Subjects who withdraw from the study before completion will not be replaced, however, they may return to the study if they choose to do so. (See 4.1.14 and 9.3).

Permanent discontinuation from study drug and dropouts must be reported to the Coordination Center within 24 hours. Subjects should, if willing, continue to be followed even if they are no longer receiving study drug.

9.2 SUBJECT RETENTION

Given the length of follow up in this study, retention is crucial to the outcome. When a subject has difficulty in adhering to the follow up schedule or drug regimen, the site coordinator will work with the subject to help address the patient's barriers to participation or medication adherence. In lieu of a missed visit alternative arrangements, such as phone visits, may be employed to obtain data after discussion with the Project Manager.

9.3 SUBJECT RE- ENTRY AFTER PREMATURE WITHDRAWAL FROM THE STUDY

9.3.1 Re-entry Activities

Subjects who prematurely withdraw but later wish to return and again participate in the study will be allowed to re-consent and resume participation assuming their health status allows for this.

Subjects will re-consent and study visits will resume using the visit windows calculated at the Screening/Baseline visit (see Section 4.1.14 for details of activities associated with re-entry).

9.3.2 Study Drug Rechallenge after re-entry into the study

Study drug rechallenge will follow the protocol Section 7.4 for Dose Rechallenge. It is up to the investigator's discretion regarding maximum dose for rechallenge, taking into account the subjects previous response to study medication and any perceived side effects during prior exposure. Subjects do not have to rechallenge and may decide to re-enter the study off drug. Rechallenge may occur at any time (see Section 7.4).

10.0 SAFETY/ADVERSE EXPERIENCES

10.1 ADVERSE EXPERIENCE (AE) DEFINITION

An adverse experience is any symptom, sign, illness, or experience that develops or worsens during the course of the study, whether or not the event is considered related to study drug.

10.2 SERIOUS ADVERSE DRUG EXPERIENCES (SAE)

A serious adverse drug experience is defined as any adverse experience that occurs at any dose that results in any of the following outcomes:

- death;
- a life-threatening adverse drug experience;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant disability/incapacity; or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include (but are not limited to) allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Reports of serious adverse drug experiences, as defined above, require immediate completion of a MedWatch form and notification (<u>within 24 hours</u> of the site's notification) to the Coordination Center Project Coordinator or Clinical Monitor whether or not the Site Investigator believes that the experience is related to study drug or is expected.

Exception from MedWatch reporting:
Effective 1/1/2011, if the subject has been permanently discontinued from study drug for at least 90 days at the time of the event and the event occurred on or after 1/1/2011, a Medwatch report <u>will not</u> be required for subjects from the U.S. **Health Canada does require reporting of SAEs even if the subject is off study drug. Thus, Canadian sites will continue to complete a MedWatch report for any SAE reported at their site.**

All serious adverse events will be reviewed by the Independent Medical monitor and the Clinical Monitor and will be reported per new FDA guidelines (September, 2010) for safety reporting in IND regulated studies.

The Investigator should record all serious adverse drug experiences that occur during the study period on the Adverse Event Log and in the appropriate source documents.

All serious adverse events that are ongoing at the conclusion of the study will be followed for a minimum of 1 month or until resolution or an appropriate end point is reached.

10.3 RECORDING OF ADVERSE EXPERIENCES

At each study visit (in-person or telephone), the subject should be questioned directly regarding the occurrence of any adverse experience since their last visit.

All adverse experiences whether observed by the Investigator and/or Coordinator, elicited from or volunteered by the subject, and whether ascribed to the study drug or not, should be recorded on the Adverse Event Log (eCRF). This will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of the experience, the severity, contributing factors, and any action taken with respect to the study drug.

This recording will commence with the institution of Screening/Baseline procedures and continue until 1 month following completion of study participation.

10.4 EMERGENCY ACTIONS

Medical emergencies must be reported to Karl Kieburtz, MD, MPH: telephone 585-275-7311. After hours to receive 24-hour pager information: telephone: 585-275-7311.

Equipment, supplies, and properly skilled medical personnel must be accessible for use in an emergency in the event of an unexpected adverse event. Subjects to be included in the study must be carefully selected and the study must be conducted in an appropriate manner. Any intentional or unintentional dose of study drug taken in excess of that prescribed must be immediately reported to the Coordination Center Project Coordinator.

Also see Section 7.3 (Coding/Emergency Drug Disclosure).

10.5 ANALYSIS OF ADVERSE EXPERIENCES

An independent, blinded monitor will evaluate serious adverse experiences.

The Data and Safety Monitoring Board (DSMB) will periodically review blinded, and if necessary, unblinded medical event data. Adverse experiences, especially SAEs such as deaths, malignancies and hospitalizations, terminations and other notifiable incidents will be tracked in real time and the DSMB alerted. If there is a significantly (< 0.05) greater incidence of a major (severe)

adverse experiences in one of the treated groups, the study may be modified after discussion with the DSMB.

11.0 STATISTICAL CONSIDERATIONS

11.1 EFFICACY ANALYSIS

All efficacy outcome measures will be analyzed under the intent-to-treat principle (ITT). For the outcomes measured at 5 years, the ITT evaluable sample will include all subjects who are randomized.

11.2 PRIMARY EFFICACY VARIABLE

The primary efficacy measures will be the Symbol Digit Modalities (verbal), Modified Schwab and England, PDQ-39 summary score, ambulatory capacity (sum of 5 UPDRS questions: falling, freezing, walking, gait, postural stability), and the final 5 year Modified Rankin value. These efficacy measures are combined using a Global Statistical Test into a single primary outcome.

11.3 PRIMARY EFFICACY ANALYSIS

The primary analysis will compare the observed mean rank-sum of the five efficacy measures above (Section 11.2) in the creatine arm to the placebo arm, adjusting for site using a nonparametric Global Statistical Test (GST) [Huang et al, 2005]. A special case of this GST is the O'Brien's GST [O'Brien, 1984]. The O'Brien test requires both treatment group and placebo group to have the same distribution, a more stringent assumption than required by the Huang GST. Only if the Huang GST is statistically significant will each univariate measure be tested via a Wilcoxon rank-sum test at the alpha 0.05 level [Tilley, 1996], providing a weak protection of alpha.

The hypotheses are:

$$H_0: GTE = 0$$
versus
$$H_A: GTE \neq 0$$

Where GTE is the Global Treatment Effect (introduced by Huang et al 2005) which equals the difference between two probabilities: the probability that treatment is better than placebo and the probability that placebo is better than treatment. The GTE has a range between -1 and 1. A GTE=0 implies no treatment effect; positive GTE implies the treatment is beneficial and negative GTE implies the treatment is detrimental. The GTE can be estimated from Huang 2005, p. 535.

11.4 SECONDARY EFFICACY OUTCOMES

Efficacy: UPDRS Parts I- IV, Beck Depression Inventory, SCOPA-COG, TFC, EuroQOL EQ-5D, and final dose of dopaminergic therapy. Secondary outcomes will be analyzed using a Wilcoxon rank-sum test (UPDRS subscores, SCOPA-COG, levodopa-equivalent dose, EQ-5D, TFC) or Chi-square test (Beck).

Health Service Utilization: Resource utilization over the 5 years will be compared with a Wilcoxon rank-sum test between the two treatment groups.

11.5 ANCILLARY ANALYSIS OF PRIMARY OUTCOME

The primary GST analysis will be redone adjusting for any baseline covariates that are imbalanced and testing for a race/ethnicity by treatment interaction and a gender by treatment interaction as well as treatment effect. Sites may be considered as a covariate.
As an ancillary efficacy analysis, a repeated measures Global Statistical Test will be conducted to test whether the creatine group had less progression over the entire length of the trial, incorporating data prior to and beyond 5 years, adjusting for any unbalances in baseline covariates [Huang, 2005].

11.6 MISSING DATA, OUTLIERS, NON-COMPLIANCE, LOST TO FOLLOW-UP

Under the ITT principle, all patients who are randomized are included in the analysis. Subjects enrolled ***after*** September 16, 2008 will be withdrawn from the study if we receive a baseline eGFR <50. Under the ITT principle, data will be imputed for these individuals.

Therefore, missing data, especially in the outcome measures, can be problematic. For the primary outcome analysis using the GST, we will impute missing data for the GST using multiple imputation [Rubin, 1987]. Based on past trials, in most cases missing data is due to dropout, thus we may assume a monotone missing mechanism. We also assume missing is at random (MAR) in our analysis. Similar methods will be employed for secondary analyses and secondary outcomes.

As a sensitivity analysis, we will also do a completers analysis. The completers analysis will include only those for whom we have efficacy data at 5 years, and for those patients who die, they will be given the worst possible score.

11.7 SAFETY ANALYSIS

11.7.1 ADVERSE EXPERIENCES/CLINICAL LABORATORY DATA

All adverse experiences and serious experiences will be summarized in terms of frequency, severity and relatedness to the study medication

using the MedDRA code. Frequency of adverse experiences except mortality will be compared using chi-square tests or Fisher's exact tests. Mortality will be compared using a log-rank test (see section 11.8.3).

11.8 INTERIM ANALYSIS

11.8.1 EFFICACY INTERIM ANALYSIS

When 25% and 50% of subjects have completed 5 years of follow-up there will be formal interim analyses of the 5-year outcome data using a GST computed using the primary efficacy measures described in an earlier section. If enrollment is completed in less than 2 years, then the second interim look (when 50% patients have completed 5 years) will not be done. An overall alpha of 0.05, (two-sided), will be distributed over the 2 or 3 looks using an alpha spending function with O'Brien Fleming type stopping boundaries. If the stopping boundary is crossed in favor of treatment, the DSMB will consider stopping the trial early for efficacy. This analysis is a guideline for the DSMB and a statistically significant result does not require that the trial be stopped.

11.8.2 FUTILITY INTERIM ANALYSIS

Stochastic Curtailment will be used to stop early in favor of the null (for futility) (Lan, Demets, Halpern, 1984). When 25% and 50% of subjects have completed 5 years of follow-up, the probability of rejecting the null hypothesis at the end of the trial (given the current 5-year outcome data) will be computed. This value of the GTE corresponds to the one year improvement in the primary efficacy measures used in computing the sample size for the GST. If the conditional power is less than or equal to 20%, then the trial may be stopped due to lack of power to show an effect [Ellenberg, 2002]. Again this analysis will be a guideline for the DSMB.

11.8.3 SAFETY INTERIM ANALYSIS

During the study, the Statistical Center will report on serious adverse events and clinically significant abnormal laboratory values to the Chair of the independent Data and Safety Monitoring Board (DSMB) on the form developed for the FDA. The Chair will determine if the full committee needs to be convened by conference call or in person. In addition to the reports of serious adverse events, written safety monitoring reports will be sent to the Chair of the DSMB (or NINDS officer) for distribution.

The DSMB will monitor Kaplan Meier Curves of the cumulative mortality rates by treatment arms (partially blinded). Testing will be done sequentially after each death occurs. If there is a significant difference (greater mortality) in either arm via a two-sided log-rank test, the DSMB will hold a conference call or in-person meeting to decide if they should fully unblind, recommend stopping the study, request additional analyses, or continue the trial for an additional period of observation.

Univariate tests for each of the primary outcome measures collected at years 1, 2, 3, and 4 (Change from baseline in Symbol Digit Modalities, Modified Schwab and England, PDQ-39, and ambulatory capacity and the annual Modified Rankin values) will be compared for creatine versus placebo via (1-sided) Wilcoxon rank-sum tests. If creatine has more progression (worse) than placebo based on one of the univariate tests, then the DSMB will be notified and will hold a conference call or in- person meeting to decide if they should recommend stopping the study, request additional analyses, or continue the trial for an additional period of observation.

12.0 SAMPLE SIZE DETERMINATION

Using available literature [Olanow et al, 2004, Kieburtz et al, 1994] and historical clinical trial data sets (CALM, PEP/PEPX) of treated PD patients (on dopaminergic therapy for a minimum of 90 days), mean and variance estimates of the annual rate of change for the primary outcome measures (listed in Section 11.2) were obtained.

Although a Global Statistical Test (GST) is the primary analysis, we powered the study such that there would be sufficient sample size for each univariate outcome measure. Under the assumption of a common dose effect the GST provides power greater than or equal to the power of any of the univariate tests [Pocock, Geller, Tsiatis, 1987].

A sample size of 549 per group (computed via EAST 3) would provide power greater than 85% to detect a 1 year improvement in the treatment arm compared to control for change from baseline in Symbol Digit Modalities, change from baseline in Modified Schwab and England ADL, change from baseline in PDQ-39 summary score, and 5 year Rankin values (alpha = 0.05, two-sided test). Likewise, this sample size would provide power greater than 85% to detect a 1.5 year improvement (difference in means of 0.383) in the treatment arm compared to control for the change from baseline in ambulatory capacity. The clinically meaningful effect sizes for these 5 measures ranged from (0.182-0.333). Using the GST, this sample size (549 per group) will provide power greater than 90% at the alternative GTE value of 0.1189.

As with most clinical studies, a certain amount of drop-ins and drop-outs (including subject withdrawal or lost-to-follow-up) can be expected. In the Phase II study only 4.5 % of subjects in the creatine arm and 6% of subjects in the placebo arm dropped out of the study before 18 months. Assuming the drop-in and drop-out rate to be 20% over 5 years, the required sample size is inflated to 860 per treatment arm to account for the expected drop-ins and drop-outs in the intent-to-treat analysis using an inflation factor described in Friedman, et al, 1998. This adjustment for dropouts does not take noncompliance (e.g. failure to fully adhere to treatment regimen) into account directly. However, the data from the published literature, used to estimate change and standard deviations, includes those who did not fully comply with their treatment regimen and thus takes some of the impact of noncompliance into account.

Power analyses have been conducted using available data on secondary outcome measures. Given a sample size of 860 per group, we will have 85% power or more to detect a difference in mean (SD) change scores of 0.29 (1.6) UPDRS mental, 0.85 (4.7) UPDRS ADL, 2.4 (12.3) UPDRS Motor, 1.27 (7) SCOPA-COG, 0.036 (0.2) EuroQOL EQ-5D, 0.636 (3.5) TFC, and a difference in the Beck Depression Scale of 0.067 percentage points. The ancillary analyses of the Huang GST adjusted for baseline imbalances and the repeat measures Huang GST would generally have greater power than the primary analysis.

13.0 REFERENCES

See Appendix A

14.0 REGULATORY AND ETHICS ISSUES

14.1 COMPLIANCE STATEMENT

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines promulgated by the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA), and any applicable national and local regulations including FDA regulations under 21 CFR Parts 11, 50, 54, 56, 312 and 314.

All procedures not described in this protocol will be performed according to the study Operations Manual unless otherwise stated. Laboratory tests/evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the Operations Manual of the central laboratory unless otherwise stated.

Subjects will be informed of the need to return all used and unused study drug sachets to the study center at each in-person study visit for accounting. Study drug compliance will be calculated by direct counting of sachets at each follow up visit. The Site Investigator will be responsible for monitoring subject compliance. A subject will be counseled on the importance of complying with the study medication if the compliance falls below 90%. In the event that a subject completely stops taking study medication, the site should continue to evaluate the subject at each scheduled visit and appropriately document the lack of compliance. Subjects will NOT be dropped from the study for lack of compliance.

14.2 INFORMED CONSENT

This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50. The CTCC must review and approve the consent form before it is submitted to the sites' Investigational Review Board (IRB) or Independent Ethics Committee (IEC) for approval, and use in the study.

In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, together with any potential hazards/risks must be read and/or explained to each subject. Each subject will sign such an informed consent form. The subject must be assured of the freedom to withdraw from participation in the study at any time.

It is the Site Investigator's responsibility to make sure that the subject and/or legal guardian understands what she/he is agreeing to and that written informed consent is obtained before the subject is involved in any protocol-defined procedures including screening procedures. It is also the Investigator's

responsibility to retain the original signed consent forms and provide each subject with a copy of the signed consent form.

14.3 INSTITUTIONAL REVIEW BOARD (IRB)/INDEPENDENT ETHICS COMMITTEE (IEC)

The Coordination Center will supply all necessary information to the site Investigator for submission of the protocol and consent form to the IRB/IEC for review and approval. The Investigator agrees to provide the IRB/IEC with all appropriate material. The trial will not begin until the Investigator has obtained appropriate IRB/IEC approval. A telephone contact/fax from the Investigator may provide initial notification of this approval. A copy of the IRB/IEC approval letter and approved consent form must be submitted to the Coordination Center.

The Site Investigator will request from the IRB/IEC a composition of the members reviewing the protocol and informed consent. Appropriate reports on the progress of this study by the Investigator will be made to the IRB/IEC and the CTCC in accordance with institutional and government regulations. It is the Investigator's responsibility to notify the IRB/IEC when the study ends. This includes study discontinuation, whether it is permanent or temporary.

The Site Investigator will discuss any proposed protocol changes with the Coordination Center Project Manager and no modifications will be made without prior written approval by the Coordination Center, except where clinical judgment requires an immediate change for reasons of subject welfare. The IRB/IEC will be informed of any amendments to the protocol or consent form, and approval (where and when appropriate) will be obtained before implementation.

14.4 PROTOCOL AMENDMENTS

Changes to the protocol should only be made by an approved protocol amendment. Protocol amendments must be approved by the study's Steering Committee, OSB, DSMB and each respective site's IRB/IEC prior to implementation, except when necessary to eliminate immediate hazards and/or to protect the safety, rights or welfare of subjects. (See Investigator's Agreement).

14.5 SUBJECT CONFIDENTIALITY

The Site Investigator must assure that the privacy of subjects, including their personal identity and personal medical information, will be maintained at all times. U.S. sites have additional privacy obligations to study subjects under the Health Insurance Portability and Accountability Act (HIPAA). On the eCRFs and other documents submitted to the Coordination Center or sponsor, subjects

will not be identified by their names, but by an identification code. Personal medical information may be reviewed for the purpose of verifying data recorded in the eCRF. This shall include all study relevant documentation including subject medical history to verify eligibility; laboratory test result reports; admission/discharge summaries for hospital admissions occurring while the subject is in the study; and autopsy reports for deaths occurring during the study (where available). This may be done by the monitor, properly authorized persons on behalf of the sponsor and the Coordination Center, or regulatory authorities. Personal medical information will always be treated as confidential.

15. DOCUMENTATION

15.1 STUDY FILE AND SITE DOCUMENTS

The Site Investigator should have the following study documents accessible for review during the study.

1. Signed Form FDA 1572
2. *Curriculum vitae* (signed and dated) for Investigator and staff listed on Form FDA 1572
3. The signed IRB/IEC form/letter stating IRB/IEC approval of protocol, consent forms, and advertisement notices, documentation of the IRB/IEC composition, and all IRB/IEC correspondence including notification/approval of protocol amendments, notification of serious adverse events to the IRB/IEC, and IRB/IEC notification of study termination
4. IRB/IEC approved consent form (sample) and advertisements
5. Signed protocol (and amendments, where applicable)
6. Signed subject consent forms
7. Worksheets and source documents in support of eCRFs
8. Site Signature Log with names, signatures, initials and functional role of all persons completing eCRF
9. Copies of laboratory reports/printouts
10. Any source data/records not kept with the subject's hospital/medical records
11. Drug Log
12. Laboratory accreditation and relevant laboratory reference ranges
13. Signed and dated receipt of supplies
14. Record of all monitoring visits made by study monitor(s)
15. Copies of correspondence to and from the Coordination Center
16. Creatine Brochure
17. Certificate for Human Subject Protection Program
18. Any other documentation as required by the Coordination Center

The Site Investigator must also retain all printouts/reports of tests/procedures, as specified in the protocol, for each subject.

This documentation, together with the subject's hospital/medical records, is the subject's SOURCE DATA for the study.

15.2 MAINTENANCE AND RETENTION OF RECORDS

It is the responsibility of the Site Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. Site Investigators will be instructed to retain all study records required by the Coordination Center and federal regulations in a secure and safe facility with limited access for one of the following time periods based on notification from the Coordination Center.

The Site Investigator will be instructed to consult with and provide advance written notice to the Coordination Center before disposal of any study records and to notify the Coordination Center of any change in the location, disposition, or custody of the study files. No study document or image should be destroyed without prior written agreement between the Coordination Center and the Site Investigator.

Regulations require retention for:

- A period of at least two years after notification from the Sponsor that a U.S. NDA (New Drug Application) has been approved for the indication that was investigated or 15 years according to International Conference on Harmonization (ICH) guidelines.

- If no NDA is filed or approved for such indication, a period of at least two years after the investigation is completed or discontinued, and the FDA (Food and Drug Administration) has been notified by the Sponsor.

Electronic Records:

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study. If for some reason a site is unable to utilize the EDC System at their site, they will be allowed to be a paper-based CRF site. The data will be keyed and then batch loaded into the same database as those sites using EDC. At the conclusion of the study, a PDF (portable document format) file on electronic media depicting eCRFs for each site will be provided for record keeping. This will be provided so that sites do not need to print out paper forms. In the event of an audit, the eCRFs can be printed.

15.3 QA AUDITS/SITE VISITS

15.3.1 DURING THE STUDY

During the course of the study and after it has been completed it is likely that one or more study site visits will be undertaken by authorized representatives of the study.

The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a subsequent audit by any regulatory authority.

If such audits are to occur they will be prearranged with the site and conducted within a reasonable time frame.

15.3.2 CLOSEOUT VISIT

Following the completion of the study, Study Monitor(s) may conduct a closeout visit to ensure that all data queries have been resolved, any protocol deviations are documented appropriately, relevant study data has been retrieved, that study drug and clinical supplies have been/will be properly returned to the Coordination Center, disclosure envelopes are sent back to the Clinical Materials Services Unit, and that the Site Investigator has copies of all study-related data/information on file.

15.4 REGULATORY INSPECTIONS

The study site may be inspected by regulatory agencies, such as the Food and Drug Administration (FDA). These inspections may take place at any time during or after the study and are based on the local regulations, as well as ICH guidelines.

15.5 DATA MANAGEMENT

An Internet accessible Electronic Data Capture (EDC) system for data management will be utilized for this study. The EDC system is designed to ensure timeliness and accuracy of data as well as the prompt reporting of data from the study on an ongoing basis to the study principal and co-Investigators. The system is compliant with relevant FDA regulatory requirements per 21 CFR Part 11.

The Statistical Center will be responsible for design of the randomization scheme, creation of analytic databases, and the statistical analysis plan. Data management staff at the Coordination Center will be responsible for all data collection procedures.

Data will be securely transferred to the Statistical Center. Once the Statistical Center and the Coordination Center, in conjunction with the principal Investigator, agree that all queries have been adequately resolved and the database has been deemed "clean", the database will be officially signed off and deemed locked. All permissions to make changes (append, delete, modify or update) the database are removed at this time.

All site personnel and Coordination Center staff will remain blinded as to treatment assignments until the conclusion of the entire study. The treatment assignments are not part of the Coordination Center electronic database. The Statistical Center will have access to the treatment assignments and will not communicate about study-related matters to any other staff involved in the study.

16. INVESTIGATOR/SITE

This study will be conducted under the supervision and direction of the Investigator(s) listed in Section 1 of the Form FDA 1572. Sub-Investigators are listed in Section 6 of the Form FDA 1572. The study will be conducted at the address(es) listed in Section 3 of the Form FDA 1572.

Clinical supplies will be sent to the address listed in Section 3 of the Form FDA 1572 unless the Investigator specifies a different address to the Coordination Center. The Investigator must not conduct the study at any sites other than the one(s) stated on the Form FDA 1572.

The protocol, informed consent form, recruitment and advertisement notices will be approved by the IRB/IEC listed in Section 5 of the Form FDA 1572.

Each Site Investigator is responsible for providing copies of the protocol and all other information relating to the pre-clinical and prior clinical experience, which were furnished to him/her, to all physicians and other study personnel responsible to them who participate in this study. The Site Investigator will discuss this information with them to assure that they are adequately informed regarding the study drug and conduct of the study. The Site Investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities.

17. STUDY MONITORING

17.1 COORDINATION CENTER MONITORING STAFF

Coordination Center personnel with primary responsibility for this study are:

Study Principal Investigator:
Karl Kieburtz, M.D., MPH
Clinical Trials Coordination Center (CTCC)
Center for Human Experimental Therapeutics
University of Rochester
Rochester, New York
(585) 275-0553

Project Managers:
Irenita Gardiner, RN, CCRC
Jennifer Harman, PhD, CCRP
Clinical Project Managers
Clinical Trials Coordination Center (CTCC)
Center for Human Experimental Therapeutics
University of Rochester
Rochester, New York
Irenita Gardiner Phone: 585-703- 3401
Jennifer Harman Phone: 585-276-5629

Authorized individuals in compliance with Good Clinical Practice (GCP) and applicable regulations will monitor all aspects of the study. The Monitors will review, on a regular basis, the progress of the study with the Investigator and other site personnel.

17.2 INDEPENDENT MEDICAL MONITORING

Independent Medical Monitor
Janis Miyasaki, MD, FRCPC
Toronto Western Hospital, Univ Health Network
399 Bathurst Street MC 7-402
Movement Disorders Centre
Toronto ON M5T 2S8 CANADA
Work Phone: 416-603-6422
Fax Number: 416-603-5004
E-mail: miyasaki@uhnres.utoronto.ca

The independent medical monitor will review all serious adverse events in real time to determine relatedness to study drug.

17.3 STUDY COMMITTEES

17.3.1 STEERING COMMITTEE

The Steering Committee (SC) is composed of the Principal Investigators from the Coordination Center and Statistical Center, NINDS Program Director, three

Site Investigator members, and a Site Coordinator member. The site members serve on a rotating basis. The SC in conjunction with site Investigators are responsible for the design of the study protocol and analysis plan, and oversees the clinical trial from conception to analysis and publication.

17.3.2 DATA SAFETY MONITORING BOARD

The monitoring of subject safety and data quality will follow the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials. The NINDS has appointed an independent Data Safety Monitoring Board (DSMB) that will be responsible for periodic review of the data related to adverse events throughout the trial. The frequency and format of DSMB meetings, reports, and guidelines for interim analyses will be agreed prior to study subject enrollment. Health Canada will also receive and review data safety reports annually for the duration of the study.

17.3.3 OVERSIGHT BOARD

The NINDS has appointed an Oversight Board (OSB) which serves as an expert scientific advisory group to NINDS. After study initiation the OSB will meet as needed to monitor the scientific progress of the trial.

17.3.4 MINORITY RECRUITMENT AND RETENTION COMMITTEE

This committee will be charged with the monitoring of recruitment of minorities. The committee will interface with site Investigators and Coordinators frequently throughout the trial. This committee will also monitor retention as retention is paramount to a successful trial. A separate Minority Recruitment Protocol will be implemented.

APPENDIX A

REFERENCES

REFERENCES

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APPENDIX B

PROTOCOL SYNOPSIS

NET-PD NEUROPROTECTION CLINICAL STUDY PROTOCOL SYNOPSIS (LS-1)

Study Centers	Approximately 50 Study Centers Coordinating Center – University of Rochester Statistical Center – University of Texas, Division of Biostatistics
Study Period	Planned enrollment duration: approximately 2 years (expected 2 subjects/site/month) Planned duration of study for each subject: up to a minimum 5 years or until the last subject has completed the study.
Study Population	PD patients within 5 years of PD diagnosis, treated with dopaminergic therapy (dopamine agonists or levodopa) for at least 90 days, but not longer than 2 years.
Primary Study Objective	The primary objective of the study is to determine if there is a slowing of clinical decline in PD patients defined by a combination of cognitive, physical, and quality of life measures. Active treatment will be compared to placebo control against a background of dopaminergic therapy and usual medical care.
Study Design	Multicenter, double-blind, parallel group, placebo controlled, study of outpatients receiving treatment for PD. Subjects will be equally randomized to the study arms.
Number of Subjects	At least 1,720 eligible subjects from approximately 50 sites in the US and Canada with equal numbers of subjects per arm.
Main Inclusion Criteria	1. Subject is willing and able to give informed consent and is willing to commit to long-term follow-up. 2. PD (asymmetric features including bradykinesia plus resting tremor and/or rigidity) within 5 years of diagnosis. 3. Treated/responsive to dopaminergic therapy (dopamine agonists or levodopa) for at least 90 days, but not more than 2 years.
Main Exclusion Criteria	1. Use of creatine 14 days prior to baseline or during the study. 2. Participation in other drug studies or receipt of other investigational drugs within 30 days prior to baseline. 3. History of known hypersensitivity or intolerability to creatine. 4. In the investigator's opinion, any unstable or clinically significant condition that would impair the subjects' ability to comply with long term study follow-up. 5. Other known or suspected causes of parkinsonism (e.g. metabolic, drug induced, etc.), or any significant features suggestive of a diagnosis of atypical parkinsonism. 6. Subjects with an eGFR (MDRD equation) of less than 50 mL/min/1.73m^2.
Visit Schedule	In-person visits at Baseline, months 3, 6, 12, 18 then annually beginning with month 24; telephone contacts at alternate 6-month periods beginning with

	month 30.
Primary Outcome Measure	Global Statistical Test- Modified Rankin, Symbol Digit Modalities (verbal), Modified Schwab & England ADL scale, PDQ-39, ambulatory capacity (5 UPDRS questions).
Secondary Outcomes	**1. Efficacy:** Beck Depression Inventory, final total dose of dopaminergic therapy, EuroQOL, SCOPA-COG, TFC, UPDRS; *adjusted global statistical test and adjusted repeated measures global statistical test (* adjusted for any imbalanced baseline covariates). **2. Safety** • Serious adverse experiences frequency and severity (hospitalizations, mortality, other FDA defined AEs), changes in vital signs, clinical laboratory values, and mortality. **3. Tolerability** • Number of subjects who discontinue the study treatment • Number of subjects who discontinue the study treatment due to AEs • Number of subjects who decrease dosage of study treatment due to adverse experiences. • Final dose of study medication at study conclusion.
Route and Dosage Form	Creatine: Oral; Creatine 5 gram sachets or matching placebo, mixed with fruit juice, pudding, applesauce or yogurt, administered twice a day with the morning and evening meal (~ 8 hours apart).
Sample Size Considerations	Planned at 1,720 eligible subjects (860/arm)

APPENDIX C

SCHEDULE OF ACTIVITIES
NET-PD NEUROPROTECTION Clinical Study

	Years 1-3							
ASSESSMENTS	Screening /Baseline	Month 3	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
	SB	V01	V02	V03	V04	V05	T01	V06
		+/- 7 days	+/- 7 days	+/- 14 days	+/- 14days	+/- 14days	+/- 14 days	+/-14 days
Written Informed Consent (I/C/S)	X							
Inclusion/Exclusion Criteria (I)	X							
Demographics	X							
Medical History (I/C)	X							
Family History (I/C)	X							
PD Features (I/C)	X							
Vital Signs (including body weight) (C)	X	X		X		X		X
UPDRS I-IV	X	X		X		X		X
Diagnostic Features (I)	X							
Primary Diagnosis (I)	X							
Modified Schwab and England (I)	X			X		X		X
Mod. Rankin Scale (I)	X			X		X		X
Total Functional Capacity (I)	X							
PDQ39 (S)	X			X		X		X
EQ 5-D (S)	X			X		X		X
Symbol Digit Modalities (S/C)	X			X		X		X
SCOPA-COG	X							
Beck Depression Inventory (S)	X							
Clinical Laboratory Evaluations	X	X	X	X	X	X		X
DNA Sample	X*							
Pregnancy Test	X[1]							
Supplemental Beverage Questionnaire					X			
Consent/Withdrawal of Consent for Optional Procedures (I/C)	X	X	X	X	X	X	X	X
Health Services Utilization (S)	X		X	X	X	X	X	X
Adverse Experiences (I/C)		X	X	X	X	X	X	X
Concomitant Therapy (C)	X	X	X	X	X	X	X	X
Study Medication Adherence (C)		X	X	X	X	X	X	X
Study Drug Accountability (C)			X	X	X	X		X
Dose Management		X	X	X	X	X	X	X
Randomization Call (I/C)	X							
Dispense Study Drug (C)	X		X	X	X	X	X	X
Current Medical Conditions						X[2]	X[2]	X[2]

Green highlighting – self-report instruments that may be mailed to the subject for completion 2 weeks prior to the annual visit. These should be returned during the evaluation.

* DNA sampling is an optional portion of the study. Subjects who do not participate in this sampling may con tinue to participate in the study. DNA sampling may be obtained at any time during participation.

[1] Urine pregnancy must be completed on all subjects at screening/baseline with child-bearing potential unless 2 years post-menopausal or surgically sterile.

[2] For subjects who return after premature withdrawal

[3] Per the investigator discretion.

I = Investigator completed instrument

C= Coordinator completed instrument

S= Subject completed instrument

	Years 4-8*								
ASSESSMENTS	Month 42 	Month 48+	Month 54+ 	Month 60	Final Visit	Unscheduled Visit	Final Telephone Contact	Premature Withdrawal	End of Study Visit
	T02	V07	T03	V8	FNL	(U01, U02, etc.)	FTC	PW	EOS
	+/- 14days	+/- 14days	+/- 14days	+/- 14 days	+/- 14 days				
Written Informed Consent (I/C/S)									
Inclusion/Exclusion Criteria (I)									
Demographics									
Medical History (I/C)									
Family History (I/C)				X				X	X
Vital Signs (including body weight) (C)		X		X		X		X	X
UPDRS I-IV		X		X				X	X
Diagnostic Features (I)				X				X	X
Primary Diagnosis (I)				X				X	X
Modified Schwab and England (I)		X		X			X	X	X
Mod. Rankin Scale (I)		X		X			X	X	X
Total Functional Capacity (I)				X			X	X	X
PDQ39 (S)		X		X			X	X	X
EQ 5-D		X		X			X	X	X
Symbol Digit Modalities (S/C)		X		X				X	X
SCOPA-COG				X				X	X
Beck Depression Inventory (S)				X				X	X
Clinical Laboratory Evaluations		X		X		X[3]		X	X
Health Services Utilization (S)	X	X	X	X				X	X
Consent/Withdrawal of Consent for Optional Procedures (I/C)	X	X	X	X		X		X	X
Adverse Experiences (I/C)	X	X	X	X		X		X	X
Concomitant Therapy (C)	X	X	X	X		X		X	X
Study Medication Adherence (C)	X	X	X	X				X	X
Study Drug Accountability (C)		X		X				X	X
Dose Management	X	X	X	X		X		X	X
Dispense Study Drug (C)	X	X	X	X					
OTC Creatine Use (I/C)					X				
Subject Conclusion (I)					X				
Adverse event follow up log					X				
Current Medical Conditions	X[2]	X[2]	X[2]	X[2]		X[2]			

Green highlighting – self-report instruments that may be mailed to the subject for completion 2 weeks prior to the annual visit. These should be returned during the evaluation.

* For subjects enrolled early in the trial the V07 and T03 visits will be repeated, alternating between in-person and telephone until the last subject enrolled completes 5 years of follow up.

[2] For subjects who return after premature withdrawal

[3] Per the investigator discretion.

I = Investigator completed instrument

C= Coordinator completed instrument

S= Subject completed instrument

APPENDIX D

LIST OF ABBREVIATIONS

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
ANCOVA	Analysis of Covariance
AE	Adverse Event
ALT	Alanine transaminase
BP	Blood Pressure
BUN	Blood urea Nitrogen
CBC	Complete blood count
cm	Centimeter
CRA	Clinical Research Associate
CRF	Case Report Form
CTCC	Clinical Trials Coordination Center
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GST	Global Statistical Test
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
kg	Kilogram
LOCF	Last observation carried forward

mL	milliliter
MedDRA	Medical Dictionary for Regulatory Activities
NPO	Nothing by Mouth
OSB	Oversight Board
PD	Parkinson Disease
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
RBC	Red Blood Cell Count
SAE	Serious Adverse Event
SAS®	Statistical Analysis Software
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SOP	Standard Operating Procedure
TFC	Total Functional Capacity
UPDRS	Unified Parkinson's Disease Rating Scale

APPENDIX E

PDQ-39

Draft

NET-PD LS1
QUALITY OF LIFE SCALE (PDQ39)

1 0 2 3 2

SUBJECT ID | VISIT NO. V

INITIALS | SITE NO. | VISIT DATE MM DD YYYY

Due to having Parkinson's Disease, how often during the last month have you:

Key for questions 1 - 9
0 = Never
1 = Occasionally
2 = Sometimes
3 = Often
4 = Always or cannot do at all

1.	Had difficulty doing the leisure activities you would like to do?	1.
2.	Had difficulty looking after your home, for example, housework, cooking or yardwork?	2.
3.	Had difficulty carrying grocery bags?	3.
4.	Had problems walking half a mile?	4.
5.	Had problems walking 100 yards (approximately 1 block)?	5.
6.	Had problems getting around the house as easily as you would like?	6.
7.	Had difficulty getting around in public places?	7.
8.	Needed someone else to accompany you when you went out?	8.
9.	Felt frightened or worried about falling in public?	9.

Draft

NET-PD LS1
QUALITY OF LIFE SCALE (PDQ39)

1 0 2

SUBJECT ID

3 2

VISIT NO. V

Key for questions 10 - 27
0 = Never
1 = Occasionally
2 = Sometimes
3 = Often
4 = Always

10.	Been confined to the house more than you would like?	10.
11.	Had difficulty showering and bathing?	11.
12.	Had difficulty dressing?	12.
13.	Had difficulty with buttons or shoelaces?	13.
14.	Had problems writing clearly?	14.
15.	Had difficulty cutting up your food?	15.
16.	Had difficulty holding a drink without spilling it?	16.
17.	Felt depressed?	17.
18.	Felt isolated and lonely?	18.
19.	Felt weepy or tearful?	19.
20.	Felt angry or bitter?	20.
21.	Felt anxious?	21.
22.	Felt worried about your future?	22.
23.	Felt you had to hide your Parkinson's from people?	23.
24.	Avoided situations which involve eating or drinking in public?	24.
25.	Felt embarrassed in public?	25.
26.	Felt worried about other people's reaction to you?	26.
27.	Had problems with your close personal relationships?	27.

Draft

1 0 2

NET-PD LS1
QUALITY OF LIFE SCALE (PDQ39)

3 2

SUBJECT ID | | | | | |

VISIT NO. V | | |

Key for questions 28 - 39
0 = Never
1 = Occasionally
2 = Sometimes
3 = Often
4 = Always

If you do not have a spouse or partner, please check here ☐

28.	Lacked the support you needed from your spouse or partner?	28. ☐
29.	Lacked the support you needed from your family or close friends?	29. ☐
30.	Unexpectedly fallen asleep during the day?	30. ☐
31.	Had problems with your concentration, for example, when reading or watching TV?	31. ☐
32.	Felt your memory was failing?	32. ☐
33.	Had distressing dreams or hallucinations?	33. ☐
34.	Had difficulty speaking?	34. ☐
35.	Felt unable to communicate effectively?	35. ☐
36.	Felt ignored by people?	36. ☐
37.	Had painful muscle cramps or spasms?	37. ☐
38.	Had aches and pains in your joints or body?	38. ☐
39.	Felt uncomfortably hot or cold?	39. ☐

NET-PD LS1

1 0 2	**QUALITY OF LIFE SCALE (PDQ39)**	3 2

SUBJECT ID | | | | | | VISIT NO | V | | |

A. Source of Information: 1 = Patient, 2 = Caregiver, 3 = Patient and caregiver A. ☐

APPENDIX F

BECK DEPRESSION INVENTORY

BDI®-II

Name: _____

Date of Birth: _____ Sex: _____ Date: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today.** Darken the circle beside the statement you have picked. If several statements in the group seem to apply equally well, darken the circle that has the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. **Sadness**
   - I do not feel sad. ⓪
   - I feel sad much of the time. ①
   - I am sad all the time. ②
   - I am so sad or unhappy that I can't stand it. ③

2. **Pessimism**
   - I am not discouraged about my future. ⓪
   - I feel more discouraged about my future than I used to be. ①
   - I do not expect things to work out for me. ②
   - I feel my future is hopeless and will only get worse. ③

3. **Past Failure**
   - I do not feel like a failure. ⓪
   - I have failed more than I should have. ①
   - As I look back, I see a lot of failures. ②
   - I feel I am a total failure as a person. ③

4. **Loss of Pleasure**
   - I get as much pleasure as I ever did from the things I enjoy. ⓪
   - I don't enjoy things as much as I used to. ①
   - I get very little pleasure from the things I used to enjoy. ②
   - I can't get any pleasure from the things I used to enjoy. ③

5. **Guilty Feelings**
   - I don't feel particuarly guilty. ⓪
   - I feel guilty over many things I have done or should have done. ①
   - I feel quite guilty most of the time. ②
   - I feel guilty all of the time. ③

6. **Punishment Feelings**
   - I don't feel I am being punished. ⓪
   - I feel I may be punished. ①
   - I expect to be punished. ②
   - I feel I am being punished. ③

7. **Self-Dislike**
   - I feel the same about myself as ever. ⓪
   - I have lost confidence in myself. ①
   - I am disappointed in myself. ②
   - I dislike myself. ③

8. **Self-Criticalness**
   - I don't criticize or blame myself more than usual. ⓪
   - I am more critical of myself than I used to be. ①
   - I criticize myself for all of my faults. ②
   - I blame myself for everything bad that happens. ③

9. **Suicidal Thoughts or Wishes**
   - I don't have any thoughts of killing myself. ⓪
   - I have thoughts of killing myself, but I would not carry them out. ①
   - I would like to kill myself. ②
   - I would kill myself if I had the chance. ③

10. **Crying**
    - I don't cry anymore than I used to. ⓪
    - I cry more than I used to. ①
    - I cry over every little thing. ②
    - I feel like crying, but I can't. ③

11. **Agitation**
    - I am no more restless or wound up than usual. ⓪
    - I feel more restless or wound up than usual. ①
    - I am so restless or agitated that it's hard to stay still. ②
    - I am so restless or agitated that I have to keep moving or doing something. ③

12. **Loss of Interest**
    - I have not lost interest in other people or activities. ⓪
    - I am less interested in other people or things than before. ①
    - I have lost most of my interest in other people or things. ②
    - It's hard to get interested in anything. ③

13. **Indecisiveness**
    - I make decisions about as well as ever. ⓪
    - I find it more difficult to make decisions than usual. ①
    - I have much greater difficulty in making decisions than I used to. ②
    - I have trouble making any decisions. ③

CONTINUED ON BACK

14. **Worthlessness**
- I do not feel I am worthless. (0)
- I don't consider myself as worthwhile and useful as I used to. (1)
- I feel more worthless as compared to other people. (2)
- I feel utterly worthless. (3)

15. **Loss of Energy**
- I have as much energy as ever. (0)
- I have less energy than I used to have. (1)
- I don't have enough energy to do very much. (2)
- I don't have enough energy to do anything. (3)

16. **Changes in Sleeping Pattern**
- I have not experienced any change in my sleeping pattern. (0)
- I sleep somewhat more than usual. (1a)
- I sleep somewhat less than usual. (1b)
- I sleep a lot more than usual. (2a)
- I sleep a lot less than usual. (2b)
- I sleep most of the day. (3a)
- I wake up 1-2 hours early and can't get back to sleep. (3b)

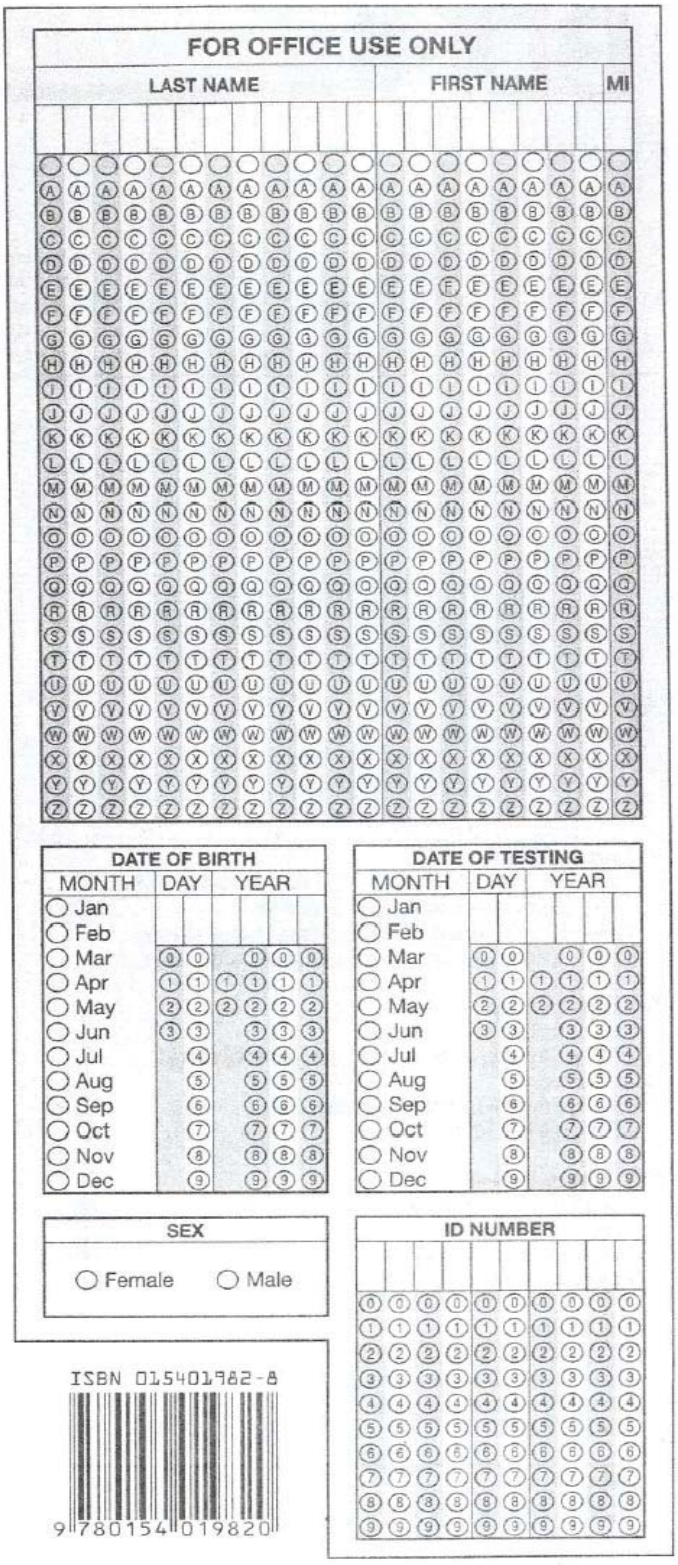
17. **Irritability**
- I am no more irritable than usual. (0)
- I am more irritable than usual. (1)
- I am much more irritable than usual. (2)
- I am irritable all the time. (3)

18. **Changes in Appetite**
- I have not experienced any change in my appetite. (0)
- My appetite is somewhat less than usual. (1a)
- My appetite is somewhat greater than usual. (1b)
- My appetite is much less than before. (2a)
- My appetite is much greater than usual. (2b)
- I have no appetite at all. (3a)
- I crave food all the time. (3b)

19. **Concentration Difficulty**
- I can concentrate as well as ever. (0)
- I can't concentrate as well as usual. (1)
- It's hard to keep my mind on anything for very long. (2)
- I find I can't concentrate on anything. (3)

20. **Tiredness or Fatigue**
- I am no more tired or fatigued than usual. (0)
- I get more tired or fatigued more easily than usual. (1)
- I am too tired or fatigued to do a lot of the things I used to do. (2)
- I am too tired or fatigued to do most of the things I used to do. (3)

21. **Loss of Interest in Sex**
- I have not noticed any recent change in my interest in sex. (0)
- I am less interested in sex than I used to be. (1)
- I am much less interested in sex now. (2)
- I have lost interest in sex completely. (3)



APPENDIX G

HEALTH SERVICES UTILIZATION

Draft

NET-PD LS1
HEALTH SERVICES UTILIZATION FOLLOW-UP

1 0 2 4 4

SUBJECT ID | 0 0 0 0 | VISIT NO. V

INITIALS | SITE NO. | VISIT DATE MM DD YYYY

1. Have you been in the hospital overnight or longer since your last visit for this study? (0 = No, 1 = Yes). If Yes, report those hospitalizations to study staff. 1.

2. Have you had any visits to an Emergency Department at a hospital not requiring an overnight stay since your last visit for this study? (0 = No, 1 = Yes). If Yes, report those hospitalizations to study staff. 2.

3. Have you seen a primary care physician since your last visit for this study? (0 = No, 1 = Yes) 3.

3.1 If Yes, how many visits? (If you have seen more than one primary care physician, give total visits to all primary care physicians). 3.1

4. Have you seen a specialist physician since your last visit for this study? (0 = No, 1 = Yes) 4.

4.1 If Yes, how many visits? (If you have seen more than one specialist physician, give total visits to all specialist physicians). 4.1

5. Have you seen a Therapist (Physical, Occupational, Speech) since your last visit for this study? (0 = No, 1 = Yes) 5.

5.1 If Yes, how many visits? (If you have seen more than one therapist, give total visits to all therapists). 5.1

6. Have you had a Home Health Visit in your home (i.e., nursing care, visiting nurse, hospice worker, health aid) since your last visit for this study? (0 = No, 1 = Yes) 6.

6.1 If Yes, how many visits? (If you have had more than one type of home health visit in your home, give total visits to all types). 6.1

7. Have you had any other visits to a Health Professional since your last visit for this study? (0 = No, 1 = Yes) 7.

7.1 If Yes, how many visits? 7.1

8. Have your medications changed since your last visit for this study? (0 = No, 1 = Yes). If Yes, report those changes to study staff. 8.

6/29/06 Page 1 of 2

Draft

NET-PD LS1
HEALTH SERVICES UTILIZATION FOLLOW-UP

1 0 2 4 4

SUBJECT ID | | | | | | 0 0 0 0 | VISIT NO. V | |

9. Where are you living now? 9. ☐
1 = Local community
2 = Retirement Center
3 = Assisted Living Facility
4 = Skilled Nursing Facility / Nursing Home

10. Due to an illness (PD or other illness), have you been forced to take time away from your usual occupation or daily activities since your last visit for this study? (0 = No, 1 = Yes) 10. ☐

10.1 If Yes, please estimate number of days. 10.1 ☐☐

11. How would you describe your current employment activities? 11. ☐
1 = Working full-time
2 = Working part-time
3 = Not working, on disability pay
4 = Unemployed and looking for work
5 = Student
6 = Retired
7 = Homemaker
8 = Other, specify: _____

6/29/06 Page 2 of 2

APPENDIX H

EUROQOL-5D (EQ-5D)

Draft

1 0 2

NET-PD LS1
EQ-5D INSTRUMENT

3 4

SUBJECT ID | 0 0 0 0 | VISIT NO. V

INITIALS | SITE NO. | VISIT DATE MM DD YYYY

Choose one statement in each group below, please indicate which statement best describes your own health state today.

1. Mobility
   1 = I have no problems in walking about
   2 = I have some problems in walking about
   3 = I am confined to bed
   1. ☐

2. Self-Care
   1 = I have no problems with self-care
   2 = I have some problems washing or dressing myself
   3 = I am unable to wash or dress myself
   2. ☐

3. Usual Activities (e.g., work, study, housework, family or leisure activities)
   1 = I have no problems with performing my usual activities
   2 = I have some problems with performing my usual activities
   3 = I am unable to perform my usual activities
   3. ☐

4. Pain/Discomfort
   1 = I have no pain or discomfort
   2 = I have moderate pain or discomfort
   3 = I have extreme pain or discomfort
   4. ☐

5. Anxiety/Depression
   1 = I am not anxious or depressed
   2 = I am moderately anxious or depressed
   3 = I am extremely anxious or depressed
   5. ☐

The EuroQol Group, EuroQol-a new facility for the measurement of health-related quality of life, *Health Policy,* 1990;16(3):199-208.

Draft

1 0 2

NET-PD LS1
EQ-5D INSTRUMENT

3 4

SUBJECT ID | | | | | |

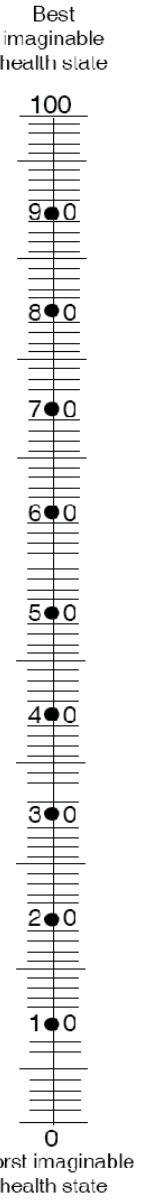
0 0 0 0

VISIT NO. V | | |

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



SCORE: | | |

The EuroQol Group, EuroQol-a new facility for the measurement of health-related quality of life, *Health Policy,* 1990;16(3):199-208.

10/2/06 Page 2 of 2

APPENDIX I

SUPPLEMENTAL BEVERAGE QUESTIONNAIRE

Supplemental Beverage Questions

	HOW OFTEN DID YOU DRINK THE BEVERAGE? (MARK ONE)									AMOUNT			
	Never or less than once per month code=0	1 – 3 per month code=1	1 per week code=2	2 - 4 per week code=3	5-6 per week code=4	1 per day code=5	2 - 3 per day code=6	4 - 5 per day code=7	6+ per day code=8	Medium serving Size	Your Serving Size S S=1	M M=2	L L=3
Decaffeinated coffee (Instant & brewed)	O	O	O	O	O	O	O	O	O	1 Cup (8 oz)	O	O	O
Instant coffee, not decaffeinated (Including flavored types)	O	O	O	O	O	O	O	O	O	1 Cup (8 oz)	O	O	O
Brewed coffee, not decaffeinated	O	O	O	O	O	O	O	O	O	1 Cup (8 oz)	O	O	O
Decaffeinated espresso and espresso drinks (Latte, Mocha, Americano)	O	O	O	O	O	O	O	O	O	1 Shot of espresso	O	O	O
Espresso and espresso drinks, not decaffeinated (Latte, Mocha, Americano)	O	O	O	O	O	O	O	O	O	1 Shot of espresso	O	O	O
Herbal or decaffeinated tea (Instant, bottled, and brewed)	O	O	O	O	O	O	O	O	O	1 Cup (8 oz)	O	O	O
Green tea (Not decaffeinated-instant, bottled, and brewed)	O	O	O	O	O	O	O	O	O	1 Cup (8 oz)	O	O	O
Black tea such as Lipton®, or Earl Grey (Not decaffeinated-instant, bottled, and brewed)	O	O	O	O	O	O	O	O	O	1 Cup (8 oz)	O	O	O
Jolt®, Surge®, Mountain Dew®, Red Bull® and other highly caffeinated sodas	O	O	O	O	O	O	O	O	O	1 Can (12 oz)	O	O	O
Regular colas and root beer (With caffeine, not diet)	O	O	O	O	O	O	O	O	O	1 Can (12 oz)	O	O	O
Diet colas and diet root beer (With caffeine)	O	O	O	O	O	O	O	O	O	1 Can (12 oz)	O	O	O
Regular colas and root beer (Caffeine free, not diet)	O	O	O	O	O	O	O	O	O	1 Can (12 oz)	O	O	O
Diet colas and diet root beer (Caffeine free)	O	O	O	O	O	O	O	O	O	1 Can (12 oz)	O	O	O

APPENDIX 1

STATISTICAL ANALYSIS PLAN

NET-PD PHASE III STUDY
LONG-TERM STUDY 1
(LS-1)

NET-PD Statistical Center
PI: Barbara C. Tilley, Ph.D.,

Jordan Elm, Ph.D., Keith Burau, Ph.D., Sheng Luo, Ph.D., Rong Ye, M.S.

The University of Texas School of Public Health
Houston, TX 77030

July 2012
Version 7

History of Changes

September 2008

- Section 3.1, 3.3, 6.12: Changes to reflect approach to analysis of those randomized who are ineligible.

June 11, 2010

- Face Page: Revised list of Statistical Coordination Center (SCC) investigators and SCC location.
- Section 4.4 - Changed to correct reference - Lan, Wittes (B. Statistic)
- Section 5.4 - Corrected typographical error ; correct version is “triangular test”.
- Section 7.5 - Added discussion of handling deaths in analysis.

March 2012

- Added section 6.1.4 plan to re-estimate the placebo rate prior to the first interim analysis.
- Section 4.2.1 Updated LED equivalency and added newer reference
- change)
- Section 6.1- Clarified the detectable treatment difference (MCID) for SDMT and ambulatory capacity corresponds to ~1.5 year change (rather than 1 year change)
- Section 7.5 –added details of plan for multiple imputation that is updated based on new methodology that takes the correlations among outcomes into account in the imputation process.

July 2012

- Removed section 6.1.4 plan to re-estimate the placebo rate prior to the first interim analysis.

1. SYNOPSIS OF THE STUDY

This is a multicenter, double-blind, Phase III study of creatine in participants with early, treated Parkinson's disease (PD). At least 1720 treated participants will be equally randomized to one of the two study arms: (1) the group that receives active creatine; (2) the group that receives placebo for creatine. Each participant will be followed for a minimum of 5 years, or until the last enrolled participant completes 5 years (maximum of approximately 7 years).

2. STUDY DESIGN AND OBJECTIVES

The study is designed to assess whether creatine slows PD clinical decline using a variety of domains. The primary 5-year outcome measures (Modified Rankin scores, Symbol Digit Modalities (verbal), Schwab and England ADL, PDQ-39 summary score, and ambulatory capacity (sum of 5 UPDRS questions: falling, freezing, walking, gait, postural stability)) will be compared in creatine versus placebo with a nonparametric Global Statistical Test (GST) (O'Brien 1984; Huang, Tilley, Woolson and Lipsitz 2005).

These outcome measures were chosen based on a consensus of the NET-PD Steering Committee comprised of five physicians specializing in movement disorders, one study Coordinator, and one Biostatistician, after consultation with the participating sites at an investigators' meeting and using input from focus groups we conducted with participants in movement disorder clinics. These measures represent simple, brief assessments of multiple dimensions of Parkinson's disease progression. The dimensions of progression being assessed include activities of daily living (Schwab and England), cognitive function (Symbol Digit Modalities), quality of life (PDQ-39), ambulatory capacity (5 UPDRS items) and an overall clinical assessment of the patient (Modified Rankin). References are given below on the validation of the measures for PD. Where the measures have been validated, but not for PD, this is noted. Similarly references are given for the secondary outcome measures, chosen through the same process as the primary outcomes.

3. DEFINITION OF TARGET POPULATION AND STUDY SAMPLES

3.1 Target Population

The target population for this study is participants with early stage PD (within 5 years of diagnosis) who meet protocol eligibility criteria, including stable treatment with dopaminergic therapy for symptomatic control of their disease (duration of dopaminergic therapy must be $\geq$ 90 days and $\leq$ 2 years). As of September 16, 2008, any newly randomized participants found to have an eGFR<50 at baseline will be discontinued from the study and will not counted toward the total number of participants needed to complete enrollment. (See also section 3.3 for discussion of Intent-To-Treat).

3.2 Rationale for Target Population

Recent PD trials enrolling early, untreated participants have shown that participants require dopaminergic therapy quickly after enrolled (almost 50% by one year) (NINDS NET-PD 2006). It is not possible to diagnose PD participants during the preclinical stage before the onset of symptoms when there is ongoing dopaminergic cell loss. We can only identify them at a point when they are very close to requiring therapy. By requiring participants to be receiving dopaminergic therapy before randomization, limiting duration of dopaminergic therapy, and limiting years from PD diagnosis, we still capture participants fairly early in their disease course.

The rationale for enrolling participants who are stably treated with dopaminergic therapy before randomization is given by Guimaraes, et al. (2005). In summary, by enrolling stably treated participants, one can minimize the variability (due to differences in timing of the initiation of dopaminergic therapy) and assume a linear rate of disease progression. Thus, fewer participants are needed for study. Variability may also be introduced due to the unequal use of dopaminergic agents during the course of the trial. The final daily dose of dopaminergic therapy required will be reported by group as a secondary outcome. Moreover,

a subset of participants will be followed out to 7 years, so that long-term complications of dopaminergic therapy can be compared between the treatment and placebo groups.

3.3 Intent-to-Treat Sample

As the primary analysis, all efficacy outcome measures will be analyzed under the intent-to-treat principle (ITT). Under this principle, the evaluable sample will include ALL participants who are randomized.

For participants randomized ***after*** September 16, 2008 who had eGFR< 50 at baseline as soon as we have obtained the baseline creatinine value, they will have their study drug discontinued and will be asked to come back into the site for a single Premature Withdrawal visit. Under the ITT principle, data will be imputed for these individuals. (See also section 7.5 for discussion of imputation).

3.4 Safety Analysis Sample

All randomized participants are included in the safety analyses.

4. EFFICACY ANALYSIS

4.1 Primary Outcome

4.1.1 Measures Used to Compute the Primary Outcome

The following measures are included in the 5-year primary outcome:

- Modified Rankin Score [van Swieten et. al., 1988; Burn 1992; Sulter et al 1999; Wilson et al 2002; Wilson et al 2005; Shinohara et al 2006 (not validated for PD)]
- Symbol Digit Modalities (verbal) score[Smith A, 1973; Sheridan 2006; Hinton-Bayre 2005(not validated for PD)]
- Schwab and England ADL [Schwab et. al., 1969; McRae 2000]
- PDQ-39 summary score [Bushnell et. al., 1999; Jenkinson et al, 1997; Peto et al 1998; Marinus et al 2002]
- Ambulatory Capacity (sum of five UPDRS items: GAIT, FALLING, FREEZING, WALKING, and POSTURAL STABILITY) [Goetz et al., 1995; Martinez Martin et al., 1994; Richards et al., 1994; Siderowf et al., 2002; Van Hilten et al., 1994].

These efficacy measures are combined using a Global Statistical Test into a **single** primary outcome.

4.1.2 Statistical Hypotheses

The statistical hypotheses are:

$$H_0: \text{GTE} = 0$$
$$\text{versus}$$
$$H_A: \text{GTE} \neq 0$$

Where GTE is the Global Treatment Effect (introduced by Huang et al 2005) which equals the difference between two probabilities: the probability that treatment is better than the placebo and the probability that placebo is better than the treatment. The GTE has a range between –1 and 1. An GTE =0 implies no treatment effect; positive GTE implies the treatment is beneficial; and negative GTE implies the treatment is detrimental. The GTE can be computed using the method given by Huang et al 2005, p. 535.

4.1.3 Primary Efficacy Analysis

The primary analysis compares the observed mean summed ranks of the five efficacy measures listed in 4.1.1 above in the creatine arm to the placebo arm. The summed ranks will be computed by ranking each

patient on each measure (across both arms) and then summing the ranks for each patient. We will use the nonparametric Global Statistical Test (GST) given by Huang, Tilley, Woolson and Lipsitz (2005). Huang et al's GST is an adjustment of O'Brien's summed ranks GST (O'Brien, 1984) in order to control the overall type I error (significance level) when two treatment groups come from different distributions (i.e. Behrens-Fisher problem). O'Brien's GST is a special case of the Huang GST when the distributions are identical. In order to adjust for site (a stratifying variable in randomization), site will be considered a random effect (see section 4.1.2).

Additionally, to interpret the outcome we will order the summed ranked data for each patient and then divide this ordered listing into quartiles. We will then compute the number (proportion) from each treatment group that appears in each quartile.

If the global statistical test is statistically significant, then each univariate measure used to compute the primary outcome will be tested using a Wilcoxon-rank sum test, at the two-sided nominal level of 0.05. We will not adjust for multiple comparisons since testing the individual measures is only done when the overall test is significant and this approach gives weak protection of alpha.

4.2 Secondary Efficacy Analyses

4.2.1 Outcomes

The secondary efficacy analyses will be used to confirm the findings based on the primary analysis. The following 5-year outcomes will be compared between treatment and placebo groups: UPDRS subscores (I-III), Beck Depression Inventory (BDI), SCOPA-COG, EuroQOL EQ-5D, Total Functional Capacity (TFC), final daily dose of dopaminergic therapy. These were measures thought to be relevant for PD that are not adequately captured in the primary analysis.

To compare with other long-term studies, the change from baseline to 5 years in UPDRS subscores will be compared between treatment and placebo groups.

The SCOPA-COG is a short, easily administered cognitive battery specifically developed for the assessment of PD cognitive impairment. This tool includes measures of attention, memory, executive function, and visuospatial abilities. This reliable scale is sensitive to cognitive changes over time suggesting its utility for detecting early cognitive changes in PD.

The EuroQOL EQ-5D was chosen since this is a generic quality of life measure. It has been validated in PD and has the added aspect of providing utilities, which will be used in the economic cost-effective analysis.

As a general overall measure of functional status, the Total Functional Capacity (TFC) has been used in Huntington's disease and was used in our 12 and 18 month futility studies. This brief scale reviews a participant's potential for occupational capacity and financial abilities, not otherwise captured.

The Beck Depression Inventory (BDI) will provide information regarding study subjects' mental health, and is simpler than the Structured Clinical Interview for the DSM. The BDI is a frequently used and validated instrument that has been shown to be sensitive to the severity of depression in PD participants. Adverse event and concomitant medication data will provide additional data on depression and antidepressant therapy use.

The final total daily levodopa-equivalent dose (mg) of will be compared between treatment groups. Levodopa-dose equivalency will be computed for dopaminergic therapy as follows (Fine et al 2000; Goetz et al 1999; Tomlinson et al 2010):

Agonist		Generic	LED conversion
Dopamine	Medication		
	MIRAPEX	Pramipexole	X100
	NEUPRO	Rotigotine	X 30
	PRAMIPEXOLE	Pramipexole	X 100
Levodopa	PRAMIPEXOLE DIHYDROCHLORIDE	Pramipexole	X 100
	REQUIP	Ropinirole	X 20
	ROGITINE	Rotigotine	X 30
	ROPINIROLE	Ropinirole	X 20
	ROPINIROLE HYDROCHLORIDE	Ropinirole	X 20
	ROTIGOTINE	Rotigotine	X 30
	SIFROL	Pramipexole	X 100
	CARBIDOPA/LEVODOPA	Levodopa	Levodopa X 1
	LEVODOPA	Levodopa	X 1
Other	LEVODOPA W/BENSERAZIDE	Levodopa	Levodopa X 1
	PARCOPA	Levodopa	Levodopa X 1
	SINEMET	Levodopa	Levodopa X 1
	SINEMET 10/100	Levodopa	Levodopa X 1
	SINEMET 25/250	Levodopa	Levodopa X 1
	SINEMET CR	Levodopa	Levodopa X 0.75
	STALEVO	Levodopa	Levodopa X 1.33
	AMANTADINE		N/A
	AMANTADINE HCL		N/A
	ARTANE		N/A
	AZILECT	rasagiline	X 100
	BENZTROPINE		N/A
	BENZTROPINE MESYLATE		N/A
	CARBIDOPA		N/A
	COENZYME Q10		N/A
	ELDEPRYL (Oral)	selegiline	X 10
	ENTACAPONE		LD x 0.33
	LODOSYN	carbidopa	N/A
	RASAGILINE		X 100

If new medications come on the market our consultant in pharmacology will determine the appropriate value for levodopa equivalence.

Listing of Articles Validating the Secondary Outcomes:

- UPDRS (I-III) [Goetz et al., 1995; Martinez Martin et al., 1994; Richards et al., 1994; Siderowf et al., 2002; Van Hilten et al., 1994]
- Beck Depression Inventory (BDI) [Beck, 1996; Visser 2006]
- SCOPA-COG [Marinus, 2003]
- EuroQOL EQ-5D [EuroQOL Group, 1990; Dolan et al, 1995; Dolan, 1997; Siderowf et al, 2002; Brazier et al, 1996; Schrag et al 2000]
- Total Functional Capacity (TFC) [Shoulson, 1989 (not validated for PD)]

4.2.2 Description of Secondary Analysis Methods

Secondary outcomes will be analyzed using a Wilcoxon rank-sum test adjusted for site and also for baseline values, where applicable. The Beck Depression Inventory will be analyzed as a binary outcome (BDI score > 17 is evidence of depression) (Chi-squared test).

The null hypothesis of no difference between creatine and placebo will be tested. Each test will be conducted at the two-sided nominal level of 0.05 as these are separate secondary analyses.

4.2.3 Additional Analyses of the Primary Outcomes

The primary analysis will be redone adjusting for any baseline covariates that are imbalanced and testing for a race/ethnicity by treatment interaction and a gender by treatment interaction.

As a secondary efficacy analysis, a repeated measures GST will be conducted to compare the groups over time incorporating data prior to and beyond 5 years. This analysis will also adjust for any baseline covariates that are imbalanced and adjust for site.

4.2.4 Exploratory Analyses

These exploratory analyses will compare change in UPDRS over time between the treatment and placebo groups as a further assessment of treatment benefit. Several important disease features will be captured via the annual UPDRS evaluations. For example, the development of motor complications, including fluctuations and dyskinesias, and hallucinations are not evaluated via the other measures.

For the UPDRS over time, a repeated measures analysis will be conducted of the overall total score (Parts I-III). A linear mixed model including a random effect for subject will be used to compare treatment groups.

The development of motor complications will be defined as the time from randomization to the first occurrence of disabling dyskinesias (UPDRS Q32>0 AND UPDRS Q33>0) or wearing off (fluctuations) more than 25% of the day (UPDRS Q39>0). A Cox proportional hazard regression will be used to compare treatment groups to determine if creatine can delay the onset of motor complications.

A repeated measures logistic regression analysis (using GEE) of the occurrence of hallucinations (UPDRS Q2 > 1) will be conducted to compare treatment groups.

In addition, new methods developed by Huang, Chen, and Sinha (2006) will be used to compare groups on the onset of postural instability defined through a latent process model. This approach will take the multiple occurrences of the outcome over time into account.

4.3 Interim Analysis for Efficacy

When 25% and 50% of participants have completed 5 years of follow-up there will be formal interim analyses of the five-year outcome computed using the GST based on the primary efficacy measures described in Section 4.1.1. If enrollment is completed in less than 2 years, then the second interim look (when 50% participants have completed 5 years) will not be done. An overall alpha of 0.05 (two-sided) will be distributed over the 2 or 3 looks using an alpha spending function with O'Brien Fleming type stopping boundaries. The appropriate ITT sample (i.e. 25%, 50% or 100% of total sample) will be used for the interim and final analyses. If the stopping boundary is crossed in favor of treatment, the DSMB will consider stopping the trial early for efficacy. This analysis is a guideline for the DSMB, and a statistically significant result does not require that the trial be stopped.

4.4 Interim Analysis for Futility

Stochastic Curtailment will be used to stop early in favor of the null (for futility) (Lan KKG, Simon R, Halpern M. 1982; Lan, Wittes 1988). When 25% and 50% of participants have completed 5 years of follow-up, the conditional power (given the current 5-year outcome data and computed at an alternative value of the GTE =0.1189) will be computed. This value of the GTE corresponds to the one year to 1.5 year improvement in the primary efficacy measures used in computing the sample size for the GST. If the conditional power is less than or equal to 20%, then the trial may be stopped due to lack of power to show an effect (Ellenberg 2002). Again this analysis is a guideline for the DSMB. Tang, Geller, Pocock 1993 indicate that sequential methods can be applied to GSTs.

5. SAFETY ANALYSES

5.1 Adverse Events, Serious Adverse Events, and Deaths

All adverse events and serious adverse events, including deaths, will be summarized by body systems in terms of frequency, severity, and relatedness to the study drug using the MedRA code. The following specific adverse events will also be summarized:

- Nausea, vomiting, or dyspepsia
- Skin reaction
- Headache
- Muscle pain
- Renal insufficiency

At the conclusion of the study, the summary tables will be presented by treatment group. Frequency of adverse events will be compared using chi-square tests or Fisher's exact tests.

5.2 Laboratory Measures

Summary statistics of lab values are reported by lab type. At the conclusion of the study, the mean lab values for total WBC, Hemoglobin, Hematocrit, Platelets, and all Chemistry labs will be presented by treatment group.

5.3 Medication Tolerability

All occurrences of dose reductions, suspensions and premature terminations of study medication due to AEs are monitored. Summary statistics of these occurrences are reported by AE. At the conclusion of the study, the tabulation will be presented by treatment group.

5.4 Safety Interim Analyses

The DSMB will monitor Kaplan Meier Curves of the cumulative mortality rates by treatment arms (partially blinded). Testing will be done sequentially after each death occurs. If there is a significant difference (greater mortality) in either arm via a two-sided triangular test, the DSMB will hold a conference call or in-person meeting to decide if they should fully unblind, recommend stopping the study, request additional analyses, or continue the trial for an additional period of observation. Adjustments for the multiple looks will be controlled by PEST v4 software. A triangular test will be used with overall alpha prespecified at 0.05 (Whitehead, 1997).

Univariate tests for each of the primary outcome measures collected at years 1, 2, 3, and 4 (Change from baseline in Symbol Digit Modalities, Schwab and England, PDQ-39, and ambulatory capacity and the annual Modified Rankin values) will be compared for creatine versus placebo via (1-sided) Wilcoxon rank-sum tests, using a uniform stopping boundaries of $p \leq 0.005$. This p-value corresponds to $p<0.025/5$ (one-sided alpha, bonferroni correction for the 5 univariate tests). These tests will begin when 500 participants (250 per group) have completed 1 year of follow-up and will be repeated every 6 months (using all available participants' data) for each year of follow-up (except year 5). If creatine has more progression (worse) than

placebo based on one of the univariate tests, then the DSMB will be notified and will hold a conference call or in- person meeting to decide if they should recommend stopping the study, request additional analyses, or continue the trial for an additional period of observation. Since this is a safety analysis there is no adjustment for multiple comparisons due to the interim looks within and across years.

6. SAMPLE SIZE DETERMINATION

6.1 For the Primary Analysis

6.1.1 Assumptions

Using available literature (Olanow et al 2004; Kieburtz et al. 1994) and historical clinical trial data sets (CALM, PEP/PEPX) of treated PD participants (on dopaminergic therapy for a minimum of 90 days), mean and variance estimates of the annual rate of change for the primary outcome measures (listed in Section 4.1.1) were obtained. Although a GST is the primary analysis, we powered the study such that there would be sufficient sample size for each univariate measure used to compute the primary outcome.

The minimum clinically meaningful difference was chosen to be a 1 year improvement in each measure, meaning that at 5 years the treatment arm progression is equivalent to progression in the placebo group at 4 years. Thus, progression (based on each measure) has been slowed by 1 year.

Estimates of Placebo and Treatment Means and Standard Deviation Used for Sample Size Calculations

Measure	Placebo mean	Treatment mean	1 year Difference in means	Common Standard Deviation	Clinically Meaningful Effect Size	Source:
PDQ-39 Summary score Change from baseline to 5 year	15	12	3	9	0.333	Olanow et al. 2004
Modified Rankin final 5 year value	2.2	2	0.2	1	0.200	FS1/FS2/K. Shannon, (unpublished data)
Schwab and England ADL Change from baseline to 5 year	10	8	2	11	0.182	PEP/PEPX
Ambulatory capacity Change from baseline to 5 year	1.25	0.92	0.33**	2.11	0.152	CALM-PD
Symbol-Digit Modalities Change from baseline to 5 year	5.5	4	1.5**	8.0	0.188	Kieburtz et al. 1994

**See section 6.1.2

In computing the sample size, we assumed a linear change in slope over 5 years. If this assumption is not correct, it would be likely that participants worsen at a faster rate in later years. Assuming the pooled standard deviation remains the same, we would be comparing to a control mean representing a more rapid progression, the magnitude of the difference between groups could increase under the same assumption of a one year difference (creatine at year 5 equals placebo at year 4), and our power would be as least as great as we estimated.

6.1.2 Adjusting Sample Size for Drop-ins/Drop-outs

A sample size of 549 per group (computed via EAST 3) would provide power greater than 85% to detect a 1 year improvement in the treatment arm compared to control for change from baseline in Schwab and England ADL, change from baseline in PDQ-39, and 5 year Modified Rankin values (alpha = 0.05, two-sided test). Likewise, this sample size would provide power greater than 85% to detect a ~1.5 year improvement in the treatment arm compared to control for the change from baseline in ambulatory capacity (difference in means of 0.383) and change from baseline in Symbol-Digit Modalities (difference in means of 1.5). Using GST, this sample size (549 per group) will provide power greater than 90% at the alternative GTE value of 0.1189 (the GTE is estimated based on Huang et al 2005, p 535).

As with most clinical studies, a certain amount of drop-ins and drop-outs (including participant withdrawal or loss-to-follow-up) can be expected. Assuming the drop-in and drop-out rate to be 20% overall, the required sample size is inflated from 549 to 860 per treatment arm to account for the expected drop-ins and drop-outs in the intent-to-treat analysis using an inflation factor described in Friedman, et al (1985). This inflation factor for noncompliance is $R=1/(1-p)^2$, where p is the proportion of expected drop-ins and drop-outs. While the drop-in rate is unknown, the drop-out rate in FS1 (using data from the placebo and creatine arms only) was low. In this Phase II study, only 4.5% of participants in the creatine arm and 6% of participants in the placebo arm dropped out of the study before 18 months. This adjustment for drop-outs does not take noncompliance (e.g. failure to fully adhere to treatment regimen) into account directly. However, the data from the published literature, used to estimate change and standard deviations, includes those who did not fully comply with their treatment regimen and thus, takes some of the impact of non-compliance into account.

As of September 16, 2008, any newly randomized participants found to have an eGFR<50 at baseline will be discontinued from the study and will not count toward the total number of participants needed to complete enrollment.

6.1.3 Re-estimating Variance

We used the largest variance observed for each outcome for our variance estimates. Some of our observed variance estimates may be smaller because of rigorous standardization of the physician-completed outcome measures. It is also possible that the variance estimates used here for sample size calculations are underestimates of the variance we actually observe. To determine if this is the case, after 75% of participants have completed 1 year of follow-up we will compare our 1 year estimates of variance to those used for the sample size calculations (without unblinding) (Gould 1992, 1995). If the observed variance of the 1-year outcomes is greater than that value used in the sample size calculations, then the DSMB will be asked to determine if the magnitude of the difference warrants an increase in sample size, implying enrollment should be continued (or restarted).

6.2 Power for the Secondary Analyses

For the analysis of the primary outcome adjusting for baseline covariates and for the repeated measures analysis of the primary outcome, we should, in general, have power greater than or equal to the power of the primary outcome at 5 years. The test for gender and race/ethnicity interactions will be performed at the 0.1 level. We have no preliminary data to estimate the magnitude of this interaction computed and the power of the GST but reducing the critical level for testing will make it less difficult to detect an interaction. If interactions are detected, there would also be reduced power to test for a treatment effect within sub-groups and results will be presented as confidence intervals on the treatment effect.

Power analyses have been conducted using available data on univariate secondary outcome measures. Given a sample size of 860 per group, we will have 85% power or greater to detect the following difference in means:

Secondary Outcome	Detectable Mean Difference in 5 Yr Chg scores (treatment vs. placebo)	Assumed Common Standard Deviation	Effect Size	Source
UPDRS Mental	0.29	1.6	0.182	CALM
UPDRS ADL	0.85	4.7	0.182	CALM
UPDRS Motor	2.24	12.3	0.182	CALM
SCOPA-COG	1.27	7.0	0.182	Marinus et al 2003
EuroQol EQ-5D	0.036	0.2	0.182	CALM
Total Functional Capacity (TFC)	0.636	3.5	0.182	FS1/FS-TOO
Dopaminergic therapy	N/A	N/A	0.182	N/A

N/A = not available

For the Beck Depression Inventory, analyzed as a binary outcome (>17), given a sample size of 860 per group, we will have 85% power or greater to detect a difference in proportions of 0.20 versus 0.133, where the proportion is the percent depression. The placebo rate was from Schrag 2002.

7. GENERAL STATISTICAL CONSIDERATIONS

7.1 Participant Accountability

Prior to any statistical analysis, every participant randomized into the study will be accounted for in terms of analysis samples.

7.2 Randomization

The treatment for each participant will be assigned by a randomized code. A stratified (with site as the stratifying variable) blocked randomization scheme (using a SAS® program) will be used to ensure approximately even distribution of participants into the two treatment groups at each participating site. The block size will be randomly chosen.

The randomization algorithm prepared by the Statistical Center and participant enrollment process will be implemented through the Internet accessible Electronic Data Capture (EDC) system using authenticated, password-protected accounts for each study site. The EDC system will automatically validate inclusion/exclusion criteria. For the eGFR eligibility criteria, this eligibility information is not available at the time of randomization because incorporating a separate screening visit would increase burden on the patient, the site staff, and increase the overall cost of the trial. As of Sept 16, 2008, if eGFR does not meet the eligibility criteria, we discontinue those randomized individuals who are ineligible as soon as we have obtained the creatinine value and calculated eGFR (see section 3.3).

7.3 Blinding

The study is to be conducted in a double-blind manner. The participants and site investigators will be blinded to the treatment assignment. Furthermore, staff at the CTCC will also be blinded. Staff at the Statistical Center will be partially blinded*, i.e.,* they will know that a participant belongs to a particular treatment arm, but not whether or not that arm is receiving active or placebo drug. Staff at the Central Pharmacy will be completely unblinded. The placebo for the investigational drug will be identical to the investigational drug in appearance. Drug packages will be identical in appearance with the exception of the drug package code number affixed to the outside of the package. At the request of the DSMB, the Statistical Center will be able to break the blind for the DSMB.

7.4 Multiplicity

There is a single primary outcome measure computed from the GST from multiple measures (listed in Section 4.1.1). Thus there is not an issue of multiplicity for the primary outcome. Only if the global statistical test is statistically significant will each univariate measure used in defining the primary outcome be tested at the alpha 0.05 level. This provides weak protection of alpha. Group sequential methods (O'Brien and Fleming) will be used to control for interim analysis of efficacy analyses. For secondary outcomes and safety analyses, no adjustment of Type I error probability will be considered, since they will be treated as exploratory.

7.5 Missing Data

Under the ITT principle, all randomized participants are included in the analyses (primary and secondary) regardless of the treatment they actually received, drop-out, or withdrawal of consent. Therefore, missing data in the outcome measures needs to be imputed.

For participants enrolled ***after*** September 16, 2008 who had eGFR< 50 at baseline as soon as we have obtained the baseline creatinine value, they will have their study drug suspended and will be asked to come back into the site for a single Premature Withdrawal visit. Prior to Sept 16, 2008, 5.5% of participants were enrolled who had an eGFR<50 at baseline. Given this rate, we expect ~40 participants will be randomized after Sept 16, 2008 who are ineligible due to eGFR. Under the ITT principle, data will be imputed for these individuals.

Every effort will be made to keep missing data to a minimum (See section 6.1.3 for a discussion of dropout rates). In the event that, despite the sites' best efforts, there are missing data in the primary outcomes, then for the primary outcome analysis, we will impute missing data using the multiple imputation method proposed by Luo et al (2010). Specifically, the proposed imputation model based on item response theory (IRT) account for all sources of correlation among the multivariate longitudinal outcomes across visits, i.e., inter-source (different measures at same time point), intra-source (same measure at different time points), and cross correlation (different measures at different time points) (O'Brien 2004). The inference based on the GST and GTE is combined using Rubin's multiple imputation rules (Rubin 1987). Based on past trials, in most cases missing data is due to dropout, thus we may assume a monotone missing mechanism. We also assume missing is at random (MAR) in our analysis. Similar methods will be employed for secondary analyses where a GST is used. For secondary outcomes that are composed of a single measure of efficacy, missing data will be imputed by multiple imputation (SAS PROC MI) (Rubin 1987).

Participants who have died will be given the worst outcome score for each outcome or the score for death if such a score is part of the scale (SMDT=0, mRS=6, PDQ-39=100, ambulatory capacity=20, SEADL=0).

As a sensitivity analysis we will also do a completers analysis. The completers analysis will include only those for whom we have efficacy data at 5 years, and for those participants who die, they will be given the worst possible score.

7.6 Statistical Methods

The analytical approaches we are using are in a field that is under development. Prior to the 3 year interim analysis of the primary outcome, if new methodology becomes available that will enhance the methods proposed then they may be adopted. If this occurs then this Statistical Analysis plan will be revised.

7.7 Treatment Group Comparability

7.7.1 At Baseline

Summary statistics for the following baseline variables will be computed and compared between treatment groups.

Demographic:

- Mean age
- Gender
- Race (some categories with small frequencies will be combined)
- Ethnicity
- Mean years of education
- Education category: 0-12 (up through high school), 12 and greater

PD characteristics:

- Mean time since symptom onset
- Mean time since diagnosis

Medical history:

- Presence of pulmonary disorder, disease or surgery in the past

- Presence of cardiovascular disorder, disease or surgery in the past
- Presence of hepatobiliary disorder, disease or surgery in the past
- Presence of gastrointestinal disorder, disease or surgery in the past
- Presence of hemato-lymphatic disorder, disease or surgery in the past
- Presence of dermatological disorder, disease or surgery in the past
- Presence of renal disorder, disease or surgery in the past
- Presence of urological disorder, disease or surgery in the past
- Presence of gynecologic disorder, disease or surgery in the past
- Presence of ophthalmological disorder, disease or surgery in the past
- Presence of ear, nose, throat disorder, disease or surgery in the past
- Presence of musculoskeletal disorder, disease or surgery in the past
- Presence of metabolic or endocrine disorder, disease or surgery in the past
- Presence of neurological (other than PD) disorder, disease or surgery in the past
- Presence of psychiatric disorder, disease or surgery in the past
- Presence of allergy or immunological disorder, disease or surgery in the past

Physical examination and vital signs:

- Handedness: left, right, mixed
- Mean height
- Mean weight
- BMI
- Mean systolic blood pressure (supine and standing)
- Mean diastolic blood pressure (supine and standing)
- Mean pulse

Outcome measures at Baseline:

- Mean UPDRS part I-IV scores
- Mean Modified Rankin score
- Mean Schwab & England score
- Mean Symbol Digit Modalities score
- Mean PDQ-39 summary score
- Percent Beck Depression Inventory (BDI) > 17
- Mean Total Functional Capacity (TFC) score
- Mean EuroQOL EQ-5D score
- Mean SCOPA-COG score

7.7.2 At Study Conclusion

Summary statistics for the baseline variables listed above will be presented comparing those who are included and excluded from the completers only sample within each treatment arm as well as for the overall study. The statistical tests for comparison will be two-sample t-test or Wilcoxon rank sum test for continuous scale variables and chi-square or exact test for categorical variables.

7.8 Site Effects

On average, approximately 35 participants are anticipated to be enrolled at each site, although there will be some variability in the number of participants enrolled per site. The sites are diverse geographically and culturally and have differing levels of experience in clinical trials. Thus it is important to adjust for a site effect in randomization.

7.9 Participant Compliance

A participant is considered compliant with study medication if he/she reported at least medium compliance on the study adherence questionnaire (where medium is scored according to the algorithm provided in Morisky et al 1986). According to the FS1 and FS-TOO results, in general, medium compliance corresponded with more than 80% compliance as measured by study drug counts. The medication compliance data will be obtained from the Compliance and Drug Label CRFs, as well as the Compliance Questionnaire CRF.

8. ECONOMIC STUDY

8.1 Purpose

The aim of modeling cost-effectiveness is to provide information to inform medical or health policy decision making processes. The primary aim of the economic substudy is to determine whether creatine is cost-effective, provides cost-savings, or is cost-neutral at 60 months compared to placebo. If creatine has greater clinical effectiveness at a lower cost, and the measure of effectiveness is clinically compelling, the decision is clear. If creatine has a slightly higher clinical effectiveness at a substantially higher cost, then the discussion of the advantages and disadvantages of adopting this intervention should be informed by data on the incremental cost effectiveness (or value of the money expended) of the new therapy compared to currently used approaches. Furthermore, the type of economic study proposed allow projection of the changes in the level and allocation of expenditures to expect as one or more new therapies get adopted. It is important for third party payers to understand if part or all of a potential increase in their drug expenditures will be partially or fully offset by a decrease in expenditures for hospital or long term care services. The planned economic analysis will enable us to answer these questions in a timely manner for the trial interventions.

8.2 Economic Analysis Plan

Costs will be retrieved every 6 months. While attempts will be made to include all health care costs, costs of Parkinson's disease can be expected to dominate over a 60-month period. The reason for including all costs is that it is sometimes difficult to distinguish PD-related from non-PD-related events. However, every attempt will be made to separate hospitalizations and office visits associated with a subject's PD problems from non-PD episodes of care. The type of office visit and follow-up hospitalization will be based on participant reporting and allow evaluation of both total and PD specific costs. In addition, the effectiveness of each treatment group (active vs. placebo) through clinical endpoints and quality of life (EuroQOL EQ-5D) measures will be examined. A cost-effectiveness analysis will be used to compare the treatment groups at 12, 24, 36, 48, and 60 months in dollars per QALY gained. Standard cost-effectiveness methodology will be used as recommended by the task force of experts organized by the U.S. Public Health Service (PHS) (Gold et al, 1996). For the cost-effectiveness analysis, the mean costs for each arm will be used in the numerator and the mean QALY of each treatment arm will be used in the denominator. The median costs and QALYs will also be employed as an alternative estimate of the cost-effectiveness ratio. These analyses will provide the best estimates of the cost-effectiveness of active vs. placebo over each 12-month period. The results of the economic analyses may be used by health care decision makers to compare the cost-effectiveness of creatine therapy to other health care interventions.

As a secondary analysis, an econometric model (Lee et al, 1997; Mauldin et al, 1999; Jeong et al, 2005) to assess the cost-effectiveness within the study at months 12, 24, 36, 48, and 60 will be developed. This model will permit assessment of the cost-effectiveness using multiple outcome measures and for subgroups in a multivariate manner not possible with standard cost-effectiveness analysis. Interaction terms will be included in the analysis. They will capture the separate effect of, for example, creatine alone on subgroups of participants identified by specific exogenous variables. If it turns out that the average results suggest that creatine is more effective, the interaction terms could identify certain types of participants who benefit more than average without creatine. If, for example, the interaction term of age is sufficiently positive, it would imply that older participants receive a smaller decline of health without creatine than with creatine, other things being equal. The intent of this approach is to systematically define and analyze how the clinical and

subject variables interrelate to obtain a better understanding of which factors are most powerful or the best predictors in explaining treatment costs and outcomes. By systematically analyzing the major factors which contribute to the cost and outcomes of alternative therapies and comparing these results on the dimensions of time, sample subsets, and variable subsets, not only will the overall understanding of the relationship between the cost and outcomes of these therapies be illuminated, but it will also systematically evaluate which combinations of variables are most appropriate and useful.

Thus, the cost, cost/effectiveness, econometric analyses should be seen as complementary forms of analysis, with the econometric model looking internally within the NET-PD LS-1 clinical study, and the cost-effectiveness and cost analyses providing our most generalizable measures to other illnesses.

8.3 Valuation of Participant Survey Response Events

8.3.1 Primary Method for Resource Utilization - Archival Billing Databases

Patient-oriented resource utilization data will be linked to NET-PD LS-1 Clinical Study clinical data and a set of standard cost weights developed from archival billing data sources from participants with Parkinson's disease. The resources reported by the study participants (including medications) will be converted to dollar values (a proxy for opportunity cost) using standard cost weights as follows: 1) medications will be valued according to the Red Book Average Wholesale Price (AWP) value, 2) as a common unit of measure, health care services cost weights will be constructed using charges from the South Carolina (SC) Medicaid program, and hospital admissions records from both the national Hospital Cost and Utilization Project (HCUP) database and the SC Medicare database, and 3) the opportunity cost of missed days from work will be estimated based on participants' self-report of income range and missed days. The SC Medicaid database includes billing data for all Medicaid participants. This data set includes all billing data elements for provider visits, outpatient surgeries, hospital admissions, nursing home stays, and prescription drug coverage. The State of SC manages this unique database, which merges Medicaid, State Employee, Provider, and Geographical Information System (GIS) data and will serve as part of a comprehensive database for the construction of cost weights for this proposal.

The SC Medicare database and national HCUP database will also be used to construct cost weights for our model. The Medicare dataset comprises claims for SC residents aged 65 and older. The Medicare data include claims from inpatient hospitals, physician/suppliers, outpatient-care facilities, skilled nursing facilities (SNFs), home health agencies, and hospice care. HCUP is a family of healthcare databases and related software tools and products developed through a Federal-State-industry partnership and sponsored by the Agency for Healthcare Research and Quality (AHRQ). HCUP includes the largest collection of longitudinal hospital care data in the United States, with all-payer, discharge-level information beginning in 1988. HCUP databases contain discharge-level information compiled in a uniform format with privacy protections in place. The Nationwide Inpatient Sample (NIS) includes inpatient data from a national sample of over 1,000 hospitals. The State Inpatient Databases (SID) cover inpatient care in community hospitals in participating States that represent approximately 85 percent of all U.S. hospital discharges. The State Ambulatory Surgery Databases (SASD) contain data from ambulatory care encounters.

For the NET-PD LS-1 Clinical Study, events and Episodes-of-Care will be constructed from the SC Medicaid, Medicare and national HCUP databases by ICD-9 or 10 codes and appropriate cost weights applied to the clinical and follow-up data for study participants. These data will be used to provide regional comparisons of costs, as well as provide ranges appropriate for preliminary sensitivity analysis. All cost estimates will be made in constant dollars, with the adjustment factor being the medical component of the Consumer Price Index (CPI). Discounting of costs and QALYs will be necessary and a rate of 3% will be applied to estimates for months greater than 12.

8.3.2 Secondary Method for Resource Utilization-Literature for Sensitivity Analysis.

To gain further insight into the variation in the resource utilization and costs of the NET-PD LS-1 Clinical Study, several sensitivity analyses will be performed. Sensitivity analysis involves systematically altering our assumptions about the cost and effectiveness of the creatine approach to therapy compared to placebo. Two types of sensitivity analyses will be performed. The first set of calculations will be one-way sensitivity

analyses. In one-way sensitivity analysis, the assumption about each parameter is varied over a reasonable range of values with all other parameters fixed. Specifically, we will vary one-by-one our estimates of the different cost components over the 60-months of follow-up. Robust estimates from the literature will be used to provide ranges (Noyes et al, 2005; Whetten-Goldstein, et al, 1997; John Robbins Associates, 1998; Tanner & Goldman, 1996). These estimates, and others mentioned above, will provide credible values to test the sensitivity of our estimates. The 25th and 75th percentiles for each parameter will be used as the range for one-way sensitivity analysis. Finally, favorable and unfavorable scenarios will be developed for the study participants based on various assumptions. Because the specifics of these scenarios will depend on the nature of the findings, these analyses cannot be fully described a priori. Nonetheless, these scenarios will reflect the understanding of the variation surrounding the cost estimates and the correlations among those parameters. Thus, extensive sensitivity analyses will be performed to test robustness of the findings concerning the costs of the alternative arms in the NET-PD LS-1 Clinical Study.

8.3.3 Determining Utility Weights - Valuation of the EuroQol EQ-5D

Valuation of the health states as determine by the EuroQol EQ-5D will be based on the scientifically accepted indexed values determined by Dolan (1995; 1997). Dolan's model predicted the mean values for 42 EuroQOL EQ-5D health states in terms of level of severity associated with each dimension of the survey. Once study participants complete the EQ-5D survey at baseline and each 12-month follow-up visit, responses will be entered into the database and the mean values will be applied to their responses for an appropriate valuation of their health state.

8.4 Statistics

Cost data will be displayed in tables to highlight the extent to which costs cluster around outpatient costs, non-healthcare patient costs (i.e. wheelchairs), medications and admission(s). Costs will also be displayed graphically in a cumulative fashion, with cost on the horizontal axis and percent of participants with a specified or lower cost on the vertical axis. Finally costs will be displayed for each 12-month period, with months on the x-axis and mean cost on the y-axis. Outcome data (i.e., QALYs) will be presented graphically as cumulative distribution plots for each 12 months, with mean and median points noted. A Student's t-test will be used to compare the values over their respective time periods of direct observation of the 2 arms of the NET-PD Neuroprotection Clinical Study. If, however, the QALYs deviate substantially from a normal distribution, a Wilcoxon Rank Sum test will be used.

Means and standard deviations of costs will be presented for each component of cost. "Trimmed" means and standard deviations of costs will be presented when 10% largest values and 10% smallest values are ignored. This way the summary statistics are less influenced by the small number of extreme outliers. Another possibility is to consider median as a measure of location and inter-quartile range as a measure of variance. However, the usual or trimmed means and standard deviations seem more appropriate for this analysis because health care providers and payers may be concerned more about average cost, not median cost. It is expected that a log transformation will be used for the multivariable analysis cost comparison between the two study groups.

The number of participants who will be enrolled in the NET-PD LS-1 Clinical Study has been chosen based on the power required to detect a clinically significant difference between the treatment arms. Since creatine has the potential to slow the functional decline in PD participants, it would not be ethical to enlarge the study sample size in order to enhance the ability to detect economic differences. Furthermore, several economic parameters will be measured that together will be used to describe the expected economic differences between the two therapies. Assuming that by 5 years the creatine treatment group is 1 year less severe than placebo, a cost savings, or at least cost neutrality by 60 months is a very desirable economic outcome, given the study population. Thus, the study's power to identify 10% savings in cost at 60 months for the creatine treatment group, compared to the placebo treatment group will be examined. Data from a prior study on a sample of 39 S.C. Medicaid participants who had an ICD-9 code consistent with PD (332.0 n=39) coded on an outpatient visit bill indicate that the average annual cost (*proxied by Total Charges submitted to Medicaid*) for participants with PD was $14,960 in 2000. The study's power to detect differences with 860 subjects per arm (alpha=.05 and a 2 sided test) is estimated below.

Table 2: Power for Economic Analyses

ICD-9 Codes:	332.0 n=39
Mean Annual Cost	$14,960
Standard Deviation*	$8,320
Reduction in Cost (10%)	$1,496
Percent Power	96%

** assuming that control variables explain 50% of the variance in total costs*

Previous cost regressions of clinical trial data from participants with complex chronic conditions have shown that baseline control variables can explain at least 50% of the variance in the annual cost for these types of participants. Given that the clinical study has 860 subjects in each arm, at least 95% power to identify a 10% cost difference is expected.

The bootstrap technique (Efron & Tibshirani, 1993; Chaudhary & Stearns, 1996) will be used to assess the variation in the cost effectiveness ratios estimated from the study data to obtain a 90% Confidence Interval (CI) around the estimated costs. This technique is appropriate when costs are estimated from the recorded resource use data combined with the standard costs weights.

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