NET-PD LARGE STUDY-1 PROTOCOL SYNOPSIS (LS-1)

Study Centers	Approximately 52 Study Centers Coordinating Center – University of Rochester Statistical Center – Medical University of South Carolina
Study Period	Planned enrollment duration: approximately 2 years (expected 2 participants/site/month) Planned duration of study for each participant: up to a minimum 5 years or until the last participant 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. Participants will be equally randomized to the study arms.
Number of Participants	At least 1,720 randomized participants from approximately 52 sites in the US and Canada with equal numbers of participants per arm.
Main Inclusion Criteria	1. Participant 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 participants' 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.
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), 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 event frequency and severity (hospitalizations, mortality, other FDA defined AEs), changes in vital signs, clinical laboratory values, and mortality. 3. **Tolerability** • Number of participants who discontinue the study treatment • Number of participants who discontinue the study treatment due to AEs • 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 participants (860/arm)

	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**	**V06**	**V07**
Written Informed Consent (I/C/S)	X							
Inclusion/Exclusion Criteria (I)	X							
Demographics	X							
Medical History (I/C)	X							
Vital Signs (including body weight) (C)	X	X		X		X		X
UPDRS I-IV	X	X		X		X		X
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	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 Sampling	X*							
Pregnancy Test	X[1]							
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			X	X	X	X		X
Randomization Call (I/C)	X							
Dispense Study Drug (C)	X		X	X	X	X	X	X
Participant Disposition (I)								

Green highlighting – self-report instruments that may be mailed to the participant 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. Participants who do not participate in this sampling may continue to participate in the study. DNA sampling may be obtained at any time during participation.

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

[2] For participants enrolled early in the trial who will continue until all participants complete 5 years of follow-up.

[3] Per the investigator discretion.

I = Investigator completed instrument

C= Coordinator completed instrument

S= Participant completed instrument

	Years 4-5						
ASSESSMENTS	**Month 42** 	**Month 48[2]**	**Month 54[+]** 	**Month 60**	**Final Visit**	**UV**	**Premature Withdrawal**
	V 08	**V09**	**V10**	**V11**	**V99**		**PW**
Written Informed Consent (I/C/S)							
Inclusion/Exclusion Criteria (I)							
Demographics							
Medical History (I/C)							
Vital Signs (including body weight) (C)		X		X	X	X	X
UPDRS I-IV		X		X	X		
Schwab and England (I)		X		X	X		
Mod. Rankin Scale (I)		X		X	X		
Total Functional Capacity (I)				X			
PDQ39 (S)		X		X	X		
EQ 5-D		X		X	X		
Symbol Digit Modalities (S/C)		X		X	X		
SCOPA-COG				X			
Beck Depression Inventory (S)				X			
Clinical Laboratory Evaluations		X		X	X	X[3]	X
Health Services Utilization (S)	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[2]	X		X
Randomization Call (I/C)							
Dispense Study Drug (C)	X	X	X	X[2]			
Participant Disposition (I)				X	X		X

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

[2] For participants enrolled early in the trial who will continue until all participants complete 5 years of follow-up.

[3] Per the investigator discretion.

[+] Telephone contacts will continue at 6 month periods throughout duration of trial (Months 66, , Month 78, etc.)

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