Effect of Creatine Monohydrate on Clinical Progression in Patients With Parkinson Disease
A Randomized Clinical Trial

Writing Group for the NINDS Exploratory Trials in Parkinson Disease (NET-PD) Investigators

**IMPORTANCE** There are no treatments available to slow or prevent the progression of Parkinson disease, despite its global prevalence and significant health care burden. The National Institute of Neurological Disorders and Stroke Exploratory Trials in Parkinson Disease program was established to promote discovery of potential therapies.

**OBJECTIVE** To determine whether creatine monohydrate was more effective than placebo in slowing long-term clinical decline in participants with Parkinson disease.

**DESIGN, SETTING, AND PATIENTS** The Long-term Study 1, a multicenter, double-blind, parallel-group, placebo-controlled, 1:1 randomized efficacy trial. Participants were recruited from 45 investigative sites in the United States and Canada and included 1741 men and women with early (within 5 years of diagnosis) and treated (receiving dopaminergic therapy) Parkinson disease. Participants were enrolled from March 2007 to May 2010 and followed up until September 2013.

**INTERVENTIONS** Participants were randomized to placebo or creatine (10 g/d) monohydrate for a minimum of 5 years (maximum follow-up, 8 years).

**MAIN OUTCOMES AND MEASURES** The primary outcome measure was a difference in clinical decline from baseline to 5-year follow-up, compared between the 2 treatment groups using a global statistical test. Clinical status was defined by 5 outcome measures: Modified Rankin Scale, Symbol Digit Modalities Test, PDQ-39 Summary Index, Schwab and England Activities of Daily Living scale, and ambulatory capacity. All outcomes were coded such that higher scores indicated worse outcomes and were analyzed by a global statistical test. Higher summed ranks (range, 5-4775) indicate worse outcomes.

**RESULTS** The trial was terminated early for futility based on results of a planned interim analysis of participants enrolled at least 5 years prior to the date of the analysis (n = 955). The median follow-up time was 4 years. Of the 955 participants, the mean of the summed ranks for placebo was 2360 (95% CI, 2249-2470) and for creatine was 2414 (95% CI, 2304-2524). The global statistical test yielded $t_{1865.8} = -0.75$ (2-sided $P = .45$). There were no detectable differences ($P < .01$ to partially adjust for multiple comparisons) in adverse and serious adverse events by body system.

**CONCLUSIONS AND RELEVANCE** Among patients with early and treated Parkinson disease, treatment with creatine monohydrate for at least 5 years, compared with placebo did not improve clinical outcomes. These findings do not support the use of creatine monohydrate in patients with Parkinson disease.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00449865

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Parkinson disease is a progressive neurodegenerative disorder that affects approximately 6 million people worldwide and more than one-half million individuals in the United States.1 Parkinson disease–associated morbidity and mortality in the United States contribute $6 billion to health care costs annually.2 Incidence of Parkinson disease is expected to increase over the next decade, but neither a cure nor a treatment is available that has been proven to slow progression. Identification and development of effective therapies for slowing progression of Parkinson disease is a research priority.

In 2001, the National Institute of Neurological Disorders and Stroke (NINDS) created the NINDS Exploratory Trials of Parkinson Disease (NET-PD) program to evaluate therapies to slow the progression of disability. The sponsor used 3 major advisory groups, the Committee to Identify Neuroprotective Agents for Parkinson (CINAPS),3 an Oversight Board, and an independent data and safety monitoring board (DSMB) to guide the operational elements of the NET-PD program. The program consisted of multiple operational groups: a statistical coordinating center, a clinical coordinating center, and a network of 45 clinical investigative sites in the United States and Canada (academic medical centers and Parkinson disease specialty centers). NET-PD investigators and the advisory groups applied CINAPS criteria (preclinical criteria for predicted safety, tolerability, and efficacy)3 to select 4 compounds for study. Futility trials,4-6 which identify compounds unlikely to have therapeutic benefit, were used to narrow the list of candidate compounds for future efficacy trials and to reduce resource commitments.7

Of the 4 compounds, only creatine monohydrate (creatine) was not found to be futile, based on a modified futility analysis of 2 clinical trials.4-6 The NINDS recommended that the NET-PD program evaluate creatine in a large, long-term trial (Long-term Study 1 [LS-1]) of individuals with early, stable Parkinson disease receiving dopaminergic therapy, testing the hypothesis that 5 years of creatine (10 g/d) would slow the rate of clinical disease progression by 1 year, as compared with placebo.

**Methods**

LS-1 was a multicenter, double-blind, parallel-group, placebo-controlled, 1:1 randomized efficacy trial. Participants were randomized to creatine or placebo within each site (45 total sites). Randomly chosen block sizes were used to approximately balance treatment assignments over time. Randomization lists were generated by the Statistical Coordination Center and provided to the central drug processing unit, which used the list to sequentially process unit packages of drug or placebo for distribution to sites. Sites remained blinded to treatment assignment through the use of a central computer-based randomization module to match drug kit with a randomized participant. Complete details on the trial rationale, eligibility criteria, outcome measures, sample size justification, and approach to analyses have been published8; the study protocol is available in Supplement 1. A summary is presented below.

**Intervention**

Participants received creatine monohydrate (5 g) or placebo, dispensed as identical 7-g sachets, and the contents were mixed with food and taken twice a day. Investigators, those collecting the data, and participants were unaware of the treatment assignment. All investigators were blinded to creatinine levels and estimated glomerular filtration rate (eGFR) (only the DSMB had access to actual values).

**Study Recruitment and Retention**

Enrollment occurred from March 13, 2007, to May 28, 2010. Eligible participants were fewer than 5 years from Parkinson disease diagnosis (defined as asymmetric features including bradykinesia plus resting tremor, rigidity, or both) and had taken levodopa or a dopamine agonist for at least 90 days but not longer than 2 years. Continuation of other prescribed Parkinson disease therapy was allowed. Participants were to be followed up for a minimum of 5 years or until the end of the trial (a maximum of 8 years for the first enrolled participants) and encouraged to remain in the study even if they discontinued study drug. Adjustments of Parkinson disease medication were permitted during the trial. The institutional review board(s) approved the study, the study protocol, and the informed consent process and documentation. All patients provided written informed consent.

**Primary Outcome Measure**

Comparison of clinical decline between treatment groups used a global statistical test (GST)9-9 to analyze 5 measures of Parkinson disease progression. The global outcome combined information on change from baseline in the Modified Schwab and England Activities of Daily Living Scale,10 39-Item Parkinson’s Disease Questionnaire (PDQ-39) Summary Index (PDSI),11,12 ambulatory capacity (the sum of 5 questions from the Unified Parkinson Disease Rating Scale [UPDRS]),8,13 Symbol Digit Modalities Test,14 and the modified Rankin Scale15 at 5 years in a single analysis outcome. The measures of function, activities of daily living, ambulation, cognition, and quality of life were chosen because they are generally thought to be relatively resistant to dopaminergic therapy and are the hallmarks of worsening Parkinson disease.

Secondary outcome measures included change in the total UPDRS score,13 UPDRS subscores, Scales for Outcomes in Parkinson Disease–Cognition,16 EuroQOL instrument,17 Total Functional Capacity,18 Beck Depression Inventory,19 levodopa equivalent daily dose,20 and body mass index.

**Sample Size**

As described in the design article,8 860 participants per group with 5 years of follow-up would provide 99% power to detect a 1-year difference in clinical progression using a GST,8 if such a difference existed. The prespecified difference of interest detectable with the GST was a global treatment effect9 of 0.1189, which approximately aligned with a difference of a 1-year delay in disability between the 2 treatment groups.8,21 LS-1 had 80% to 85% power for secondary analyses of the individual outcome measures of clinical progression.
Analysis
All analyses were conducted according to the intention-to-treat (ITT) principle. To compute the GST, all measures were coded such that higher values are worse (reverse coding for Modified Schwab and England Activities of Daily Living Scale and Symbol Digit Modalities Test). Next, the summed ranks for a participant were computed by ranking each participant on each measure (across both treatment groups) and then summing the ranks for each participant, such that the summed rank could range from 5 to 5 × N. The mean summed ranks for the 2 treatment groups were compared by fitting a linear mixed model of the summed ranks (dependent variable), adjusting for site as a random effect. The GST has a t-distribution. To describe trends across time, the GST was computed for each year of the trial. Secondary efficacy outcomes were reported as the difference in means (or proportions) between treatment groups, with 95% CIs. Analyses were conducted using SAS version 9.3 (SAS Institute Inc).

Analysis of Efficacy and Futility
Two planned interim analyses for efficacy were conducted after approximately 25% and 50% of the trial participants were eligible for 5 years of follow-up, adjusted for multiple testing using O’Brien-Fleming–type stopping boundaries to constrain the type I error rate at .05 (2-sided).

Interim analyses for futility were conducted using a B-statistic to compute conditional power.22 The smaller the computed value, the lower the probability of rejecting the null hypothesis (declaring a treatment benefit) at the end of the trial. Secondary efficacy outcomes were reported as the difference in means (or proportions) between treatment groups, with 95% CIs. Analyses were conducted using SAS version 9.3 (SAS Institute Inc).

Missing Values
All randomized participants in cohort 1 were included in the second interim analyses. Participants in either cohort who died prior to 5 years were given the worst possible value (Symbol Digit Modalities Test = 0, modified Rankin Scale = 6, PDSI = 100, ambulatory capacity = 20, Schwab and England Activities of Daily Living = 0), as recommended by the DSMB and sponsor (and included in the final statistical analysis plan). Remaining missing values were imputed using a multivariate method.24 Secondary efficacy outcomes are presented without imputation.

Sensitivity Analyses
Three sensitivity analyses were performed using cohort 1: (1) a per-protocol analysis among cohort 1 participants receiving treatment for at least 4 years (80% of the 5-year study time) and who completed a 5-year visit; (2) a “completers” analysis among cohort 1 participants who completed a 5-year visit regardless of treatment adherence; and (3) an ITT analysis with all missing values (including deaths) imputed using multiple imputation.

Safety Analyses
The DSMB reviewed safety analyses of all trial participants semiannually. In September 2008, the DSMB noted increasing creatinine levels and reductions in eGFR and became concerned that creatine was affecting the reliability of creatinine as a means of monitoring adverse trends in eGFR. Entry criteria were changed to exclude new participants with a baseline eGFR less than 50 mL/min per 1.73 m². Study drug was also discontinued if participants reached eGFR less than 30 mL/min per 1.73 m² or if creatinine levels doubled from the baseline value.

Adverse events were classified into modified body systems.8 For the final safety analysis, proportions of adverse events in each modified body system were compared between treatment groups using a χ² test or Fisher exact test and P value, with P < .01 considered significant. The difference in proportions of deaths between treatment groups was continually tested using a triangular test25 with overall type I error of .05.

Results
The enrollment goal of 860 participants per treatment group was attained, with a total of 1741 enrolled and a total of 1328 (75%) actively observed participants at study close. At the time of the first interim analysis (September 17, 2012), 28% of the total cohort had reached eligibility for the 5-year follow-up visit. The median follow-up time was 4 years (interquartile range, 3.4-9.4 years). The conditional power under the planned effect size specified in the original design was 0.94 and under the observed 5-year trend was 0.04. Given conflicting results for futility and the lack of safety concerns at that time, the trial was continued.

The second interim analysis was conducted on July 17, 2013, after 55% (n = 955; cohort 1) of the participants were eligible for a 5-year follow-up visit. The conditional power under the original design was 0.19 and under the observed 5-year trend was 0.001. Both assumptions met the prespecified stopping criteria (≤0.20). The observed global treatment effect was −0.02. The DSMB reviewed the data on August 27, 2013, and recommended termination of LS-1 for futility. The NINDS accepted the recommendation and notified site investigators and study participants on September 11, 2013. No additional efficacy data were collected beyond this point. The Figure depicts the CONSORT diagram for LS-1 at the time of the second interim analysis.

Table 1 reports the demographic characteristics and baseline clinical measures of all LS-1 participants by treatment group. eTable 1 in Supplement 2 reports these same variables for cohorts 1 (initial 55% enrolled) and 2 (participants enrolled later). Participants in cohort 1 were, on average, 2 years older and had been diagnosed 0.3 years earlier than those in...
cohort 2. Participants in cohort 1 had lower scores on the baseline Symbol Digit Modalities Test and PDSI. No other significant baseline differences were detected between cohorts.

Adherence

As of July 17, 2013, 668 (76%) of the 874 participants randomized to creatine and 669 (77%) of the 867 participants randomized to placebo remained in the study, but since participants were allowed to remain in the study while not receiving study drug, not all of these individuals were actively receiving treatment. Participants randomized to creatine were more likely to stop study drug (34%) vs participants randomized to placebo (26%). In some cases, stopping study drug was per protocol if participants reached eGFR less than 30 mL/min per 1.73 m² or creatinine levels doubled (n = 8 in placebo, n = 41 creatine). There was a significant difference between groups regarding time to stopping study drug (P < .001 by log-rank test). eFigure 1 in Supplement 2 displays cumulative time receiving study drug as a percentage of cumulative participant-years of follow-up (71% for creatine vs 79% for placebo).

Interim Efficacy Analysis of Cohort 1

The interim analysis of cohort 1 (n = 955) determined that the mean of the summed ranks of the GST for placebo was 2360.
Table 1. Baseline Characteristics of All LS-1 Participants (n=1741) by Treatment Group*  

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Placebo (n = 478)</th>
<th>Creatine (n = 477)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>No. (%) Mean (SD)</td>
<td>No. (%) Mean (SD)</td>
</tr>
<tr>
<td>Age, y</td>
<td>867 61.5 (9.6)</td>
<td>874 62.1 (9.7)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>867 554 (64)</td>
<td>874 569 (65)</td>
</tr>
<tr>
<td>Non-Hispanic whites, No. (%)</td>
<td>867 783 (90)</td>
<td>874 788 (90)</td>
</tr>
<tr>
<td>Parkinson disease characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since diagnosis, y</td>
<td>867 1.6 (1.1)</td>
<td>874 1.5 (1.1)</td>
</tr>
<tr>
<td>Duration of symptoms, y</td>
<td>867 3.3 (2.2)</td>
<td>874 3.2 (2.2)</td>
</tr>
<tr>
<td>Duration of symptomatic therapy, y</td>
<td>866 0.8 (0.7)</td>
<td>873 0.8 (0.7)</td>
</tr>
<tr>
<td>Total daily LEDD, mg</td>
<td>866 376 (247)</td>
<td>872 391 (241)</td>
</tr>
<tr>
<td>UPDRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>864 25.9 (11)</td>
<td>868 26.5 (11.7)</td>
</tr>
<tr>
<td>Mental</td>
<td>864 1.3 (1.4)</td>
<td>874 1.3 (1.4)</td>
</tr>
<tr>
<td>ADL</td>
<td>867 7.0 (3.8)</td>
<td>873 7.3 (4.1)</td>
</tr>
<tr>
<td>Motor</td>
<td>864 17.6 (8.1)</td>
<td>869 17.9 (8.6)</td>
</tr>
<tr>
<td>Ambulatory capacity</td>
<td>866 1.7 (1.5)</td>
<td>873 1.7 (1.5)</td>
</tr>
<tr>
<td>Modified Rankin scoreb</td>
<td>867 12.0 (1.0)</td>
<td>874 12.0 (1.0)</td>
</tr>
<tr>
<td>PDQ-39 Summary Index</td>
<td>865 13.0 (10.7)</td>
<td>873 13.5 (10.6)</td>
</tr>
<tr>
<td>Schwab and England Activities of Daily Living</td>
<td>867 91.4 (6.3)</td>
<td>873 90.9 (6.6)</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>863 44.5 (11.6)</td>
<td>873 44.4 (11.8)</td>
</tr>
<tr>
<td>Total Functional Capacity</td>
<td>867 12.1 (1.4)</td>
<td>872 12.0 (1.5)</td>
</tr>
<tr>
<td>Scales for Outcomes in Parkinson Disease-Cognition</td>
<td>863 30.5 (5.3)</td>
<td>868 30.0 (5.4)</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>867 0.8 (0.2)</td>
<td>874 0.8 (0.2)</td>
</tr>
<tr>
<td>BDI score</td>
<td>867 6.9 (5.5)</td>
<td>869 6.8 (5.6)</td>
</tr>
<tr>
<td>BDI score &gt;17, No. (%)</td>
<td>867 37 (4)</td>
<td>869 46 (5)</td>
</tr>
<tr>
<td>BMIe</td>
<td>863 27.9 (5.4)</td>
<td>868 27.9 (8.1)</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; BDI, Beck Depression Inventory; BMI, body mass index; EQ-5D, EuroQOL instrument; LEDD, levodopa equivalent daily dose; LS-1, Long-term Study 1; PDQ-39, 39-Item Parkinson’s Disease Questionnaire; UPDRS, Unified Parkinson Disease Rating Scale.

* Data as of May 5, 2014, final locked database.

b Differences in number of participants attributed to missing data.

(95% CI, 2249-2470) and for creatine was 2414 (95% CI, 2304-2524). Higher summed ranks indicate worse outcomes. The GST, adjusted for site, yielded $t_{2865.8} = -0.75$ (2-sided $P = .45$) and did not exceed the O’Brien-Fleming critical value of $\alpha = .0027$. There was no detected benefit or harm attributable to creatine at the time of LS-1 termination.

Table 2 reports the 95% CIs for each of the 5 components of the global score that make up the GST for cohort 1 at 5 years. eFigure 2 in Supplement 2 reports the GST test statistics by year of follow-up. Each time point includes any randomized participant from cohort 1 or 2 eligible for that visit. Comparing the GST to an approximate critical value of 1.96 ($t$ dis-

Table 2. Components of the Global Statistical Test by Treatment Group for LS-1 Cohort 1, Change From Baseline to Year 5*  

<table>
<thead>
<tr>
<th>Components Included in the Computation of Global Outcome</th>
<th>Treatment Group, Mean (SD)</th>
<th>Placebo (n = 478)</th>
<th>Creatine (n = 477)</th>
<th>Difference, Mean (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulatory capacity score</td>
<td></td>
<td>2.8 (5.0)</td>
<td>3.1 (5.5)</td>
<td>-0.3 (-1.0 to 0.4)</td>
</tr>
<tr>
<td>Modified Rankinc</td>
<td></td>
<td>2.1 (1.5)</td>
<td>2.2 (1.6)</td>
<td>-0.1 (-0.3 to 0.1)</td>
</tr>
<tr>
<td>PDQ-39 Summary Index</td>
<td></td>
<td>13 (23.2)</td>
<td>14.2 (23.5)</td>
<td>-1.2 (-4.2 to 1.7)</td>
</tr>
<tr>
<td>Schwab and England ADL</td>
<td></td>
<td>14.8 (26.0)</td>
<td>16.8 (28.3)</td>
<td>-2.0 (-5.5 to 1.5)</td>
</tr>
<tr>
<td>Symbol Digit Modalities Testc</td>
<td></td>
<td>4.5 (16.8)</td>
<td>4.9 (17.7)</td>
<td>-0.4 (-2.7 to 1.8)</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; LS-1, Long-term Study 1; PDQ-39, 39-Item Parkinson’s Disease Questionnaire.

* Cohort 1 includes those participants (n = 955) eligible for a 5-year follow-up visit at the time of interim analysis (July 17, 2013). Missing values are imputed.

b Placebo-treatment as reference group.

c Modified Rankin is the actual score at 5 years. All others outcomes are change from baseline to 5 years.

d Reverse coded such that higher scores indicate worse outcomes. Higher raw values are worse for all outcomes.
Table 3. Secondary Outcome Measures for Cohort 1

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Placebo</th>
<th>Creatine</th>
<th>Difference, Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean (SD)</td>
<td>No.</td>
</tr>
<tr>
<td>Total LEDD, (mean at year 5), mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>365</td>
<td>782 (408)</td>
<td>366</td>
</tr>
<tr>
<td>UPDRS (mean change)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>336</td>
<td>10.4 (13.8)</td>
<td>330</td>
</tr>
<tr>
<td>Total</td>
<td>339</td>
<td>1.1 (1.8)</td>
<td>333</td>
</tr>
<tr>
<td>Mental</td>
<td>339</td>
<td>4.0 (5.1)</td>
<td>333</td>
</tr>
<tr>
<td>ADL</td>
<td>336</td>
<td>5.3 (9.8)</td>
<td>330</td>
</tr>
<tr>
<td>Total functional capacity (mean change)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>343</td>
<td>−1.7 (2.4)</td>
<td>334</td>
</tr>
<tr>
<td>Scales for Outcomes in Parkinson disease–Cognition (mean change)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>315</td>
<td>−2.0 (4.9)</td>
<td>309</td>
</tr>
<tr>
<td>EQ-SD (mean change)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>342</td>
<td>−0.1 (0.2)</td>
<td>334</td>
</tr>
<tr>
<td>BDI score &gt;17 (at year 5), No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>335</td>
<td>8.5 (6.7)</td>
<td>329</td>
</tr>
<tr>
<td>BDI score ≥17 (at year 5), No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>335</td>
<td>29 (8.7%)</td>
<td>329</td>
</tr>
<tr>
<td>BMI, mean change&lt;sup&gt;d&lt;/sup&gt;</td>
<td>341</td>
<td>−0.4 (3.3)</td>
<td>338</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; BDI, Beck Depression Inventory; BMI, body mass index; EQ-5D, EuroQOL instrument; LDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson Disease Rating scale.

<sup>a</sup> Data reported from final interim analysis (July 17, 2013) with the exception of BMI and total LDD, which are reported from the final locked database (May 5, 2014).

<sup>b</sup> Values are means at year 5; BDI score greater than 17 is the difference in proportions at year 5.

<sup>c</sup> Values are mean change from baseline to year 5.

<sup>d</sup> Calculated as weight in kilograms divided by height in meters squared.

Discussion

LS-1, with 1741 participants, was one of the largest clinical trials for Parkinson disease to our knowledge. Creatine was initially considered because of evidence that it plays an important role in cellular energy production, which may be impaired in Parkinson disease. Deficits in complex I activity in platelets of patients with early Parkinson disease<sup>26,27</sup> and in post mortem substantia nigra pars compacta tissue of patients with more advanced disease<sup>28</sup> have been identified. Oral creatine supplementation in mice protected against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced dopamine depletion, suggesting a neuroprotective effect.<sup>29,30</sup> Additionally, preclinical and clinical evidence suggested that creatine would be well tolerated. Based on these data, the NINDS, CINAPS, oversight board, and DSMB recommended starting a futility trial. The initial futility trial of creatine showed a possible benefit in terms of the UPDRS both at 1 year<sup>4</sup> and 18 months.<sup>6</sup> The analysis of 18-month futility data<sup>6</sup> included all participants regardless of dopaminergic and other Parkinson disease therapies and showed a continuous benefit of creatine based on the total UPDRS. Yet despite the available preclinical and clinical evidence, creatine failed to slow the clinical progression of Parkinson disease as measured across 5 domains of Parkinson disease measured in the long-term clinical trial.

Although futility studies can eliminate therapies that are highly unlikely to be successful in an efficacy trial, futility studies are generally not designed with sufficient power to assess positive findings. Compounds evaluated under a mechanistic algorithm may also fail in subsequent adequately powered efficacy testing. Failure to find a treatment effect in this trial may have been related to the creatine dosage or to a change in the stage of Parkinson disease studied compared with the futility study (use of a de novo placebo group unexposed to any dopaminergic therapy in the futility study vs early in the...
Strengths of the Trial
We enrolled 1741 participants and were able to retain more than 76% in this 5-year trial at the time the study was stopped. We chose novel measures of Parkinson disease progression because we believed no single outcome measure captured the progressive disability in Parkinson disease and also used a GST to combine information from these outcomes, giving us greater than 99% power to detect treatment effects. The chosen creatine dosage of 10 g/d was generally well tolerated. Despite early concerns that creatine exposure could be associated with deterioration of renal function or weight gain, long-term creatine use did not appear to adversely affect renal function or body mass index. The stabilization in creatinine levels that followed the initial rise, in the setting of continued creatine use, suggests that the initial increase represents an artifact of treatment rather than a sudden onset of renal disease.

Limitations of the Trial
The observed annual rate of progression on the individual measures was slower than anticipated in our power analysis for Symbol Digit Modalities Test (1.5 points expected, 1 point observed) and PDSI (3 points expected, 2.5 points observed), and as expected for the other measures (Schwab and England Activities of Daily Living, 2-3 points per year; ambulatory capacity, 0.5 points per year; and Modified Rankin Scale, a doubling from 1 to 2 over 5 years). Variability in the rate of progression over 5 years was higher than anticipated, but the PDSI progression in another large Parkinson disease trial was similar. However, our failure to find a benefit was not attributable to reduced power, given the high power of the GST even in the presence of increased variability.

Second, although futility testing eliminated 3 other interventions, with only creatine demonstrating sufficient promise to go forward, creatine still did not show a benefit. We used the futility trial clinical screening approach, rather than a continued focus on assessment in animal models. A mechanistic approach would attempt to confirm that an agent engages its known molecular target and has an intended effect on downstream biology or pharmacology. We proceeded directly to a clinical approach (futility studies) because the mechanisms and molecular targets in Parkinson disease remain unclear. Until such targets are well established, the screening of compounds with futility studies without prior mechanistic studies is useful to identify clearly futile compounds. Future futility studies in cohorts of patients with early Parkinson disease may consider testing new treatments against a background of other nondopaminergic therapies such as monoamine oxi-
dase inhibitors to raise the threshold for success required to take a new treatment forward to a long-term trial. It is also possible that the study used too low a dose of creatine. Because the loss of the reliability of serum creatinine as a marker of kidney function is a likely adverse consequence of creatine use in clinical practice with older adults, we studied a total dosage of creatine (10 g/d) used in the futility study. Another dosage could have different beneficial or harmful effects; however, concerns about tolerability and masking of adverse kidney consequences limited the dosage used in the study.

Initial short-term futility studies were conducted in participants with early, untreated Parkinson disease. The initial futility studies did not enroll treated participants, because the slow rate of functional change while receiving dopaminergic treatment requires a large sample size and long follow-up, not feasible for a short-term futility study. In our trial we studied early, treated Parkinson disease because most patients with Parkinson disease would require early treatment during the course of a 5-year trial, thus making it more difficult to observe differences between groups over time. The treated phase is often associated with the most disability, and demonstrating a treatment effect during this phase would have a greater clinical and public health benefit. We also did not preclude the concurrent use of other Parkinson disease treatments, relying on randomization to provide some balance between treatment groups.

With respect to adherence, at the time of analysis 34% of participants randomized to creatine had stopped medication and 5% had stopped per protocol. Only 26% of those randomized to placebo stopped medication, and less than 1% stopped per protocol. A completers’ analysis of the subset continuing to take their medication for at least 4 years and with a 5-year visit gave results similar to analysis of the ITT cohort.

Conclusions
Among participants with early Parkinson disease and treated with background dopaminergic therapy, treatment with creatine monohydrate for at least 5 years, compared with placebo, did not improve clinical outcomes. These findings do not support the use of creatine monohydrate in such patients with Parkinson disease.

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**REFERENCES**


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