Original Investigation | CLINICAL TRIAL

A Randomized Clinical Trial of High-Dosage Coenzyme Q10 in Early Parkinson Disease
No Evidence of Benefit

The Parkinson Study Group QE3 Investigators

IMPORTANCE Coenzyme Q10 (CoQ10), an antioxidant that supports mitochondrial function, has been shown in preclinical Parkinson disease (PD) models to reduce the loss of dopamine neurons, and was safe and well tolerated in early-phase human studies. A previous phase II study suggested possible clinical benefit.

OBJECTIVE To examine whether CoQ10 could slow disease progression in early PD.

DESIGN, SETTING, AND PARTICIPANTS A phase III randomized, placebo-controlled, double-blind clinical trial at 67 North American sites consisting of participants 30 years of age or older who received a diagnosis of PD within 5 years and who had the following inclusion criteria: the presence of a rest tremor, bradykinesia, and rigidity; a modified Hoehn and Yahr stage of 2.5 or less; and no anticipated need for dopaminergic therapy within 3 months. Exclusion criteria included the use of any PD medication within 60 days, the use of any symptomatic PD medication for more than 90 days, atypical or drug-induced parkinsonism, a Unified Parkinson's Disease Rating Scale (UPDRS) rest tremor score of 3 or greater for any limb, a Mini-Mental State Examination score of 25 or less, a history of stroke, the use of certain supplements, and substantial recent exposure to CoQ10. Of 696 participants screened, 78 were found to be ineligible, and 18 declined participation.

INTERVENTIONS The remaining 600 participants were randomly assigned to receive placebo, 1200 mg/d of CoQ10, or 2400 mg/d of CoQ10; all participants received 1200 IU/d of vitamin E.

MAIN OUTCOMES AND MEASURES Participants were observed for 16 months or until a disability requiring dopaminergic treatment. The prospectively defined primary outcome measure was the change in total UPDRS score (Parts I-III) from baseline to final visit. The study was powered to detect a 3-point difference between an active treatment and placebo.

RESULTS The baseline characteristics of the participants were well balanced, the mean age was 62.5 years, 66% of participants were male, and the mean baseline total UPDRS score was 22.7. A total of 267 participants required treatment (94 received placebo, 87 received 1200 mg/d of CoQ10, and 86 received 2400 mg/d of CoQ10), and 65 participants (29 who received placebo, 19 who received 1200 mg/d of CoQ10, and 17 who received 2400 mg/d of CoQ10) withdrew prematurely. Treatments were well tolerated with no safety concerns. The study was terminated after a prespecified futility criterion was reached. At study termination, both active treatment groups showed slight adverse trends relative to placebo. Adjusted mean changes (worsening) in total UPDRS scores from baseline to final visit were 6.9 points (placebo), 7.5 points (1200 mg/d of CoQ10; $P = .49$ relative to placebo), and 8.0 points (2400 mg/d of CoQ10; $P = .21$ relative to placebo).

CONCLUSIONS AND RELEVANCE Coenzyme Q10 was safe and well tolerated in this population, but showed no evidence of clinical benefit.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00740714

JAMA Neurol. 2014;71(5):543-552. doi:10.1001/jamaneurol.2014.131
Published online March 24, 2014.

Editorial page 537

Supplemental content at jamaneurology.com

Group Information: The Parkinson Study Group QE3 Investigators/ Authors and a list of the members of the Parkinson Study Group QE3 appear at the end of this article.

Corresponding Author: M. Flint Beal, MD, Department of Neurology, Weill Cornell Medical College, New York Hospital, 525 E 68th St, New York, NY 10065 (fbeal@med.cornell.edu).

Section Editor: Ira Shoulson, MD.

Parkinson disease (PD) is a progressive neurodegenerative disorder commonly resulting in the loss of motor function, in nonmotor symptoms, and in cognitive decline. It affects 4.1 to 4.6 million people worldwide, and its prevalence is predicted to more than double by 2030.[1] Strong evidence has emerged that mitochondrial dysfunction and increased oxidative stress play a pivotal role in the pathogenesis of PD, providing a robust scientific rationale for testing potential "neuroprotectants" that target these processes.[2-4] Coenzyme Q10 (CoQ10) is a key component of the electron transport chain responsible for mitochondrial adenosine triphosphate generation, leads to decreased free radical generation, and, in its reduced form, acts as a powerful antioxidant.[5] Coenzyme Q10 levels and redox status have been shown to be altered in individuals with PD,[6] and CoQ10 has neuroprotective effects in multiple in vitro and animal models of neuronal toxicity, including the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of PD.[7] Finally, CoQ10 has shown promising clinical benefits in small human studies of progressive supranuclear palsy, Huntington disease, and Friedreich ataxia.[8-10]

A randomized, double-blind, placebo-controlled, multicenter phase II study of CoQ10 in early PD examined the effects of 300, 600, and 1200 mg/d vs placebo (all dosages, including placebo, also contained 1200 IU of vitamin E). Eighty participants were observed for 16 months or until dopaminergic therapy was required, whichever came first.[11] Coenzyme Q10 supplementation was associated with a trend toward decreased functional decline in participants (P = .09), as indicated by the change in total Unified Parkinson's Disease Rating Scale (UPDRS) score (Parts I-III) from baseline to last visit, and those assigned to receive 1200 mg/d of CoQ10 had a nominally significantly improved outcome (44% reduction) compared with those assigned to receive placebo (P = .04). Moreover, increased platelet mitochondrial complex I and II/III activities were demonstrated in participants assigned to receive CoQ10 vs those assigned to receive placebo (P = .04). Because CoQ10 is not known to provide symptomatic benefit,[12] these results suggested a possible disease-modifying effect. The QE3 study was designed to test the hypothesis that a high dose of CoQ10 would slow functional decline in early PD.

Methods

The QE3 trial (Coenzyme Q10 in Early Parkinson Disease) was a phase III multicenter, randomized, double-blind, placebo-controlled study examining the efficacy of 1200 and 2400 mg/d CoQ10 in reducing functional decline in patients with early PD who had not yet developed a disability requiring dopaminergic therapy. The primary clinical outcome was change in total UPDRS score from baseline to the 16-month visit, or to the last visit prior to development of sufficient symptoms requiring dopaminergic therapy ("end point") if this occurred earlier. Secondary outcomes included time to reach end point; changes in mental, motor, and activities of daily living UPDRS subscales[13]; changes in Modified Schwab and England activities of daily living scale; and changes in modified Rankin and symbol digit scores.

Participants were randomly assigned to receive 1200 mg/d of CoQ10, 2400 mg/d of CoQ10, or a matching placebo, each with 1200 IU/d of vitamin E. The vitamin E was used in combination with CoQ10 owing to reports that they may have synergistic antioxidant effects and that vitamin E may enhance CoQ10 absorption.

Randomization was conducted at the baseline visit within 30 days of the screening visit, which was conducted to assess eligibility and obtain consent. Eligibility criteria included being 30 years of age or older, the presence of all 3 cardinal signs of PD (rest tremor, bradykinesia, and rigidity), a modified Hoehn and Yahr stage of 2.5 or less, and no current or anticipated disability requiring dopaminergic therapy in the next 3 months. Major exclusion criteria included the use of any PD medication within 60 days of the baseline visit, the use of any symptomatic PD medication for more than 90 days, atypical or drug-induced parkinsonism, a diagnosis of PD of 5 years' or more duration, a UPDRS rest tremor score of 3 or greater for any limb, a Mini-Mental State Examination score of 25 or less,[14] and a history of stroke or other serious illness. Individuals taking certain supplements judged to influence outcome measures, neuroleptic individuals, individuals receiving dosages of vitamin E exceeding 800 IU or of vitamin C exceeding 300 mg, or individuals with substantial exposure to CoQ10 within 120 days were also excluded. Women of childbearing potential were required to use a reliable form of contraception from 60 days prior to baseline visit until 30 days after the final dose of the study drug.

Participants were then reevaluated at 1, 4, 8, 12, and 16 months, by the site investigator, for PD disability sufficient to require dopaminergic therapy and for UPDRS score. A participant judged by the site investigator to have reached the end point of disability, at or between scheduled visits, was deemed to have completed the study, and his or her total UPDRS score at that visit (prior to commencing symptomatic therapy) was taken as his or her primary outcome measure.

Safety information obtained at all study visits included data on adverse events, data from clinical laboratory studies, vital sign data, and results of general physical and neurological examinations, along with the annual results of dermatologic examinations. Adverse events, including serious adverse events, were reviewed throughout the trial by the independent medical monitor, the steering committee, and the independent data and safety monitoring board (DSMB). Provision was made for investigator-initiated temporary or permanent dose reductions or suspensions due to adverse effects.

Blood samples for CoQ10 plasma analysis were obtained at baseline and at 1, 8, and 16 months. Compliance was tracked through medication logs. Use of concomitant medications was tracked at all visits. Participants provided written informed consent and received no compensation. The protocol and consent documents were approved by institutional review boards at all participating sites.

The primary statistical analysis used analysis of covariance, with change in total UPDRS score from baseline to the

last study visit as the primary outcome measure, the baseline total UPDRS score entered as a continuous predictor, and the enrolling investigator and assigned treatment as categorical predictors.

Sites enrolling fewer than 4 participants were grouped together. Separate comparisons were made for each active dosage against placebo. A Bonferroni correction was used (and accounted for in the sample size calculations) to maintain an overall 2-sided α level of .05. Secondary outcomes were similarly analyzed. Repeated measures analyses, using data obtained at all follow-up visits, were also performed. Time to reach the end point of disability was analyzed using Kaplan-Meier plots, log-rank tests, and the proportional hazards model.

Our study was powered to detect a difference of 3.0 points in the primary outcome measure between placebo and active treatment groups. After allowance for an estimated 10% of early dropouts, and assuming a residual standard deviation of 8.0 units in the primary outcome model, a value consistent with other recent studies in early PD,[15] the required sample size was 200 participants per group, with a total of 600 participants.

Study personnel, including site investigators and coordinators, principal investigators (PIs), the steering committee, and the study biostatistician, remained blinded to treatment assignments throughout the study. The independent DSMB monitored study progress with access to unblinded data. In addition to monitoring the occurrence of adverse events, early terminations, and other study incidents, the DSMB reviewed 3 prespecified interim analyses of the primary outcome measure for efficacy (based on the first 150, 300, and 450 participants) and 1 prespecified interim analysis for futility (based on the first 300 participants). A Peto-Haybittle stopping rule, adjusted for multiple comparisons, was used for efficacy, requiring a nominal $P < .0005$ for early stopping. The futility analysis used a predictive power criterion so that an active treatment arm would be terminated if the likelihood of its demonstrating a statistically significant benefit over placebo was less than 10%.

Results

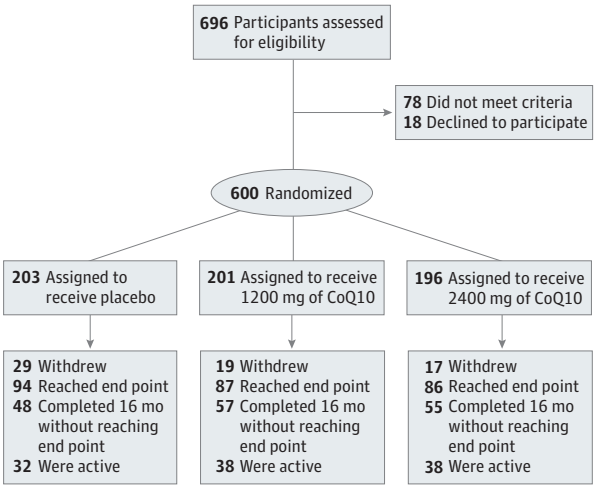
Enrollment and Participant Characteristics

Of the 696 patients with early PD who were screened, 600 were enrolled between January 2009 and October 2010 (**Figure 1**) at 67 participating Parkinson Study Group research sites (http://www.parkinson-study-group.org) (520 participants at 60 US sites and 80 participants at 7 Canadian sites). At baseline, the demographic and clinical variables were comparable across treatment groups (**Table 1**), although the placebo group was slightly younger and less impaired. The mean age of the participants was 62.5 years, the male to female ratio was 2 to 1, and the total UPDRS score at baseline was 22.8 points. A total of 45 participants (7.5%) were minorities.

Study Termination and Disposition

On April 29, 2011, the DSMB informed the PIs that both active treatment groups had reached the prespecified termination criterion for futility. Following confirmation by an independent statistician, site investigators were informed on May 6, 2011, that the study was terminating for futility. No safety concerns having arisen, active participants were so informed by site investigators and were encouraged to continue their assigned study medication until a final study visit (scheduled by June 30, 2011). The study leaders addressed participants' questions during 2 conference calls.

Figure 1. Participant Flowchart and Status at Study Termination



Status of participants on May 6, 2011. CoQ10 indicates coenzyme Q10.

Following database closeout, final clinical data analysis was conducted in December 2011. A final database of plasma levels of CoQ10 was received in October 2013. The initially reported values were in error in that they included only the oxidized CoQ10 plasma levels. The correct values of the total CoQ10 plasma level were obtained by summing the reduced and oxidized levels. This report details all safety and efficacy data collected prior to study termination. The mean follow-up time was 10.4 months.

The numbers of participants who prematurely withdrew from the study (Figure 1; eTable 1 and eFigure 1 in the Supplement) were as follows: 29 participants who received placebo, 19 participants who received 1200 mg/d of CoQ10, and 17 participants who received 2400 mg/d of CoQ10. The numerical trend toward a higher withdrawal rate in the placebo group was not statistically significant. The numbers of participants requiring symptomatic therapy were 94, 87, and 86, respectively, with no significant difference shown between groups. A total of 108 participants (32 receiving placebo, 38 receiving 1200 mg/d of CoQ10, and 38 receiving 2400 mg/d of CoQ10) were still active at study termination.

Safety

Tolerability

Coenzyme Q10 was well tolerated, with only 10 of 397 participants (2.5%) in the CoQ10 groups withdrawing owing to adverse events or drug intolerance, compared with 4 of 203 participants (2.0%) in the placebo group. In the CoQ10 groups, the adverse events leading to withdrawal that were judged to have

Table 1. Baseline Demographic and Clinical Characteristics by Assigned Treatment

Characteristic	Treatment Group			P Value
		Coenzyme Q10		
	Placebo (n = 203)	1200 mg (n = 201)	2400 mg (n = 196)	
Categorical variables, No. (%) of participants				
Male sex	130 (64.0)	139 (69.2)	128 (65.3)	.53
White race	188 (92.6)	187 (93.0)	178 (90.8)	.56
Education, y				
<9	5 (2.5)	6 (3.0)	12 (6.1)	.34
9-11	8 (3.9)	6 (3.0)	11 (5.6)	
12	29 (14.3)	30 (14.9)	30 (15.3)	
13	37 (18.2)	25 (12.4)	29 (14.8)	
14	19 (9.4)	18 (9.0)	10 (5.1)	
16	50 (24.6)	59 (29.4)	54 (27.6)	
>16	55 (27.1)	57 (28.4)	50 (25.5)	
Continuous variables, mean (SD)				
Age, y	61.3 (10.5)	63.3 (9.8)	62.8 (9.7)	.11
Age at onset, y	59.7 (10.6)	61.8 (10.2)	61.2 (9.6)	.10
Age at diagnosis, y	61.1 (10.6)	63.2 (9.9)	62.6 (9.7)	.10
Duration of PD, y	2.0 (1.5)	2.1 (1.5)	2.2 (1.9)	.40
Diagnosed, y	0.7 (0.8)	0.6 (0.7)	0.8 (0.9)	.09
UPDRS score				
Total	22.7 (9.8)	22.7 (8.4)	22.8 (8.7)	.94
Mental	0.7 (1.0)	0.8 (1.1)	0.7 (1.1)	.88
ADL	5.5 (3.2)	5.8 (2.9)	5.6 (2.9)	.54
Motor	16.5 (7.7)	16.2 (7.0)	16.4 (6.8)	.83
Hoehn and Yahr stage	1.6 (0.5)	1.7 (0.5)	1.6 (0.5)	.69
Modified SE-ADL scale	94.5 (4.8)	94.6 (4.7)	94.0 (5.3)	.84
PDQOL scale	25.5 (12.7)	25.1 (12.9)	25.9 (14.2)	.89
Modified Rankin score	1.1 (0.3)	1.1 (0.3)	1.0 (0.3)	.33
Symbol digit score	43.6 (17.0)	44.0 (16.7)	43.0 (16.4)	.76

Abbreviations: ADL, activities of daily living; PD, Parkinson disease; PDQOL, Parkinson Disease Quality of Life; SE, Schwab and England; UPDRS, Unified Parkinson's Disease Rating Scale.

a possible relation to the study drug were nausea, abdominal pain, or vomiting (2 participants); diarrhea; worsening depressive symptoms; palpitations; constipation; insomnia; and dizziness. Drug dosage was reduced for 12 participants assigned to CoQ10 (3.0%), compared with 2 participants assigned to receive placebo (1.0%), and drug treatment was suspended (temporarily or permanently) for 8.3% of participants assigned to receive CoQ10 compared with 6.4% of participants assigned to receive placebo. Compliance rates were similar across groups.

Adverse Events

Overall, 73.5% of participants reported an adverse event (mean number of adverse events, 2.3 [range, 0-19]). These events were usually mild (for 62.7% of participants) and considered unrelated to the study drug (for 59.6% of participants). There were no group differences in the number of adverse events reported, nor in the proportions of participants reporting an adverse event, a moderate or severe adverse event, or adverse events with any potential relation to the study drug (unlikely or greater). There were no clinically significant differences among treatment groups in any laboratory measure, in vital signs, or in electrocardiogram measures. **Table 2** lists the most common adverse events. Hypertension and insomnia were reported more frequently in the CoQ10 groups, but at low rates.

Serious Adverse Events

Among 33 participants, there were 41 serious adverse events. One serious adverse event, severe gastrointestinal bleeding in association with angiodysplasia, was considered to be possibly related to the study medication. Other serious adverse events that were considered unlikely to be due to CoQ10 were pulmonary embolism, atrial fibrillation, gastrointestinal bleeding, coronary artery disease, and multiple myeloma. In the placebo arm, potentially related (unlikely or greater) serious adverse events included prostatitis, exacerbation of chronic obstructive pulmonary disease, chest pain, vertigo, and elevated creatine kinase level. One death, due to a cardiac arrest 8 days after study completion, occurred in the group of participants who received 1200 mg/d of CoQ10. Four types of cancer were identified during the study: 2 types in the placebo arm (colon cancer and breast cancer) and 2 types in the CoQ10 arms (multiple myeloma and recurrence of prostate cancer).

Table 2. Adverse Events That Occurred in More Than 3% of Study Participants[a]

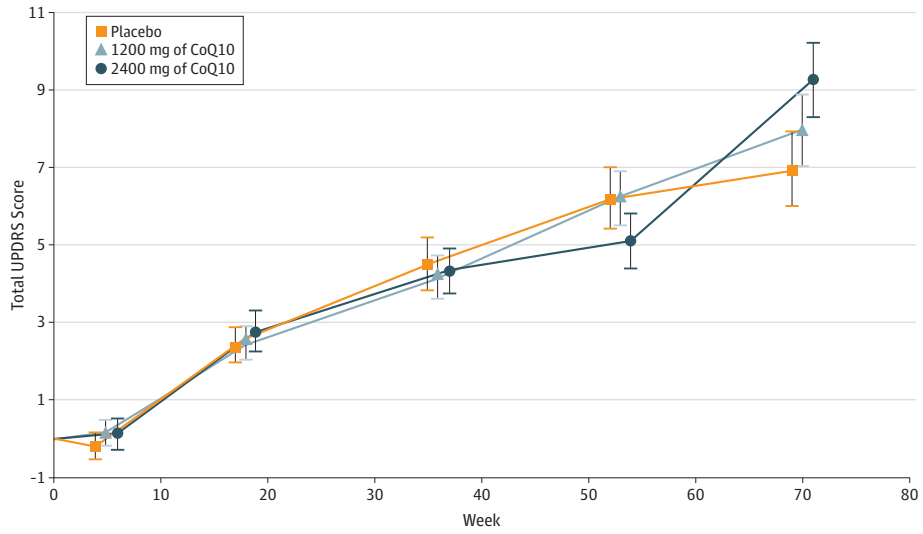
	Treatment Group, No. (%) of Participants		
		Coenzyme Q10	
Adverse Event	Placebo	1200 mg	2400 mg
Back pain	9 (4.4)	13 (6.5)	9 (4.6)
Constipation	7 (3.4)	13 (6.5)	7 (3.6)
Insomnia[b]	6 (3.0)	13 (6.5)	6 (3.1)
Anxiety	14 (6.9)	13 (6.5)	12 (6.1)
Tremor	8 (3.9)	13 (6.5)	10 (5.1)
Nasopharyngitis	3 (1.5)	9 (4.5)	7 (3.6)
Diarrhea	11 (5.4)	9 (4.5)	6 (3.1)
Headache	11 (5.4)	8 (4.0)	9 (4.6)
Urinary tract infection	3 (1.5)	8 (4.0)	6 (3.1)
Nausea	10 (4.9)	7 (3.5)	7 (3.6)
Hypertension[c]	0 (0.0)	7 (3.5)	5 (2.6)
Depression	14 (6.9)	6 (3.0)	9 (4.6)
Dizziness	5 (2.5)	6 (3.0)	7 (3.6)
Fall	7 (3.4)	6 (3.0)	6 (3.1)

[a] *P* values were calculated by use of the χ^2 test for heterogeneity. There were no statistically significant differences between treatment groups other than those indicated.

[b] *P* = .04 for insomnia of moderate/severe intensity; when including all reported cases of insomnia, the groups were not significantly different.

[c] *P* = .03.

Figure 2. Change in Total UPDRS Score From Baseline to Each Study Visit



The values shown are the mean (SE) values of the change from baseline to each visit. The total number of participants evaluated at the baseline visit and at the 1, 4, 8, 12, and 16-month visits were 600, 587, 568, 435, 322, and 229, respectively. Error bars indicate SE. CoQ10 indicates coenzyme Q10; UPDRS, Unified Parkinson's Disease Rating Scale.

Efficacy

Figure 2 shows changes from baseline to each visit in the primary outcome measure of total UPDRS score (actual data, no imputation). **Table 3** shows the results of the prespecified primary and secondary analyses; for the primary analysis, the mean total UPDRS scores increased from baseline by 6.9 (placebo), 7.5 (1200 mg/d of CoQ10; *P* = .49 relative to placebo), and 8.0 (2400 mg/d of CoQ10; *P* = .21 relative to placebo) points, showing that both active treatment groups fared slightly worse than the placebo group, although differences were not statistically significant (eTable 2 in the Supplement). The secondary outcomes also showed no benefit of CoQ10 against placebo, nor did the repeated measures analysis (data not shown; eFigure 2 in the Supplement shows the raw changes from baseline for each secondary outcome). Subgroup analyses (eTable 3 in the Supplement) showed no differences in overall findings by sex, age, or disease severity (*P* > .10 for interaction in all cases). Among the participants who reached the clinical end point of disability, the mean total UPDRS scores at end point were 35.4 (placebo), 35.2 (1200 mg/d of CoQ10), and 36.5 (2400 mg/d of CoQ10), approximately 11 points greater than at baseline and comparable across groups (eTable 4 in the Supplement). These treatment thresholds are similar to those observed in the QE2 study and other recent studies in early PD.

Compliance as judged by medication logs was generally excellent. Analyses of CoQ10 levels show clear differences between the treatment groups (eTable 5 and eFigure 3 in the Supplement), and the achieved levels for participants in the active treatment groups were in line with those anticipated.[16] Correlations between achieved blood levels and changes in total UPDRS scores from baseline were small and nonsignificant for all participants and within each treatment group (data not shown).

Table 3. Analysis of Primary and Secondary Outcome Variables[a]

Variable	Change From Baseline to Each Visit, Mean (SE)		
		Coenzyme Q10	
	Placebo	1200 mg	2400 mg
UPDRS score			
Total	6.92 (0.63)	7.50 (0.62)	8.01 (0.63)
Mental	0.41 (0.09)	0.45 (0.09)	0.60 (0.09)
ADL	2.23 (0.23)	2.76 (0.23)	2.50 (0.23)
Motor	4.23 (0.45)	4.24 (0.45)	4.88 (0.45)
Hoehn and Yahr stage	0.16 (0.03)	0.20 (0.03)	0.21 (0.03)
Modified Schwab and England ADL scale	−4.07 (0.62)	−4.29 (0.62)	−4.94 (0.62)
PDQOL scale	5.57 (0.89)	6.12 (0.87)	5.06 (0.89)
Modified Rankin score	0.40 (0.05)	0.31 (0.05)	0.38 (0.05)
Symbol digit score	−3.02 (1.48)	−0.49 (1.39)	−3.36 (1.40)

Abbreviations: ADL, activities of daily living; PDQOL, Parkinson Disease Quality of Life; UPDRS, Unified Parkinson's Disease Rating Scale.

[a] The values shown are the least squares mean (SE) values of the change from baseline to each visit, adjusted for the baseline value and the enrolling site. There were no statistically significant differences between treatment groups.

Discussion

The QE3 study tested the hypothesis that high dosages of CoQ10 could slow functional decline in early PD, as suggested by the results of the phase II QE2 study. The QE3 study was well powered to detect substantially smaller therapeutic effects of CoQ10 than those seen in the QE2 study. The CoQ10 dosages in the QE3 study included the highest dosage used in the QE2 study and an additional higher dosage, and, as in the QE2 study, included 1200 IU/d of vitamin E for all groups. Apart from the sample size, the QE3 protocol, including inclusion and exclusion criteria, closely matched the QE2 protocol. The target enrollment of 600 participants was achieved, and the participants were demographically and clinically similar to those in the QE2 study. There were no major imbalances between treatment groups regarding baseline variables, premature withdrawals, serious adverse events, or other study incidents that could explain the different results for the 2 studies. The QE3 study confirmed the safety and tolerability of high dosages of CoQ10. However, in the QE3 study, neither of the active treatment groups showed any benefit compared with the placebo group. Moreover, the adverse trend in the primary outcome measure crossed the futility threshold, leading to the termination of the study. The QE3 study therefore shows no evidence of a benefit from high dosages of CoQ10, and it fails to confirm the results of the QE2 study.

Following the completion of the QE2 study, and prior to the completion of the QE3 study, other studies have examined the effects of high-dosage CoQ10 in early untreated PD. In a randomized double-blind study that enrolled 213 patients, the National Institute of Neurological Disorders and Stroke Neuroprotection Exploratory Trials in PD (NET-PD) investigators compared the change in total UPDRS score over 1 year among the 71 patients receiving 2400 mg of CoQ10, with futility criteria established from placebo data from the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism trial.[17] The primary analysis found that CoQ10 did not meet the futility criteria. However, the applicability of this historically based criteria was criticized because practice styles and patient expectations have changed. With an adjusted futility threshold, incorporating data from the NET-PD placebo group, combined with the placebo group from Parkinson Research Examination of CEP-1347 Trial, a contemporaneous clinical trial in early PD,[15] we found that treatment with CoQ10 did appear futile. Most recently, a CoQ10 derivative, MitoQ, which has enhanced mitochondrial uptake, failed to demonstrate benefit in a randomized, double-blind, placebo-controlled 12-month clinical trial with 128 individuals with early PD.[18] These reports, combined with the definitive results of the present study, suggest that the results of the QE2 study may have been an aberration, possibly due to its relatively small size.

The plasma levels of CoQ10 in patients assigned to active treatment in the QE3 study were comparable to and, in fact, exceeded those expected in the patients from the QE2 study. The mean plasma level of CoQ10 was 5.80 µg/mL at the 16-month visit in the QE3 study for the participants who received 1200 mg/d of CoQ10 compared with 3.94 µg/mL at the 16-month visit in the QE2 study[11] and a mean level of 4.0 µg/mL observed for the same dosage in a separate pilot study.[16] In this same pilot study, the administration of 2400 mg/d produced a mean level of 7.5 µg/mL compared with 9.94 µg/mL at the 16-month visit in the QE3 study. In the QE3 study, the levels in the active treatment groups were substantially elevated over those in the placebo group and, based on the QE2 study, should have been sufficient to demonstrate clinical effectiveness.[4]

Failure to demonstrate clinical efficacy for CoQ10 in PD contrasts with predictions based on strong evidence for mitochondrial dysfunction and oxidative damage in PD pathogenesis.[2,3,19,20] It is possible that mitochondrial oxidative damage may be a consequence of other pathological processes rather than the primary cause of neurodegeneration and, therefore, that targeting this pathway would not be expected to provide benefit in PD. However, CoQ10 has demonstrated neuroprotective activity in multiple preclinical models of disease, including cell cultures and animal models of PD and other neurodegenerative diseases.[7] One problem may be optimizing administration, and how to achieve this remains to be understood. For example, ubiquinol, the reduced form of CoQ10,[21] achieves more than 3-fold higher blood levels compared with similar doses of oxidized CoQ10.[22,23] Whether coadministration of other supplements is desirable also remains to be de-

termined. In the QE3, QE2, and NET-PD studies, CoQ10 was administered in combination with vitamin E, and there is evidence from animal studies that coadministration may be beneficial.[24,25]

Significant methodological issues affect the interpretation of studies evaluating putative neuroprotective agents in early PD. The dopaminergic deficit is typically far advanced at the time of diagnosis, with upwards of 50% of the dopaminergic neurons lost and the fate of those remaining possibly already determined.[26] The optimal time to initiate a disease-modifying therapy may be before the onset of motor symptoms. The window from diagnosis to need for symptomatic therapy is short, and a growing tendency to treat earlier could affect the ability to determine a positive benefit.[27] In the CARE-HD (Coenzyme Q10 and Remacemide Evaluation in Huntington's Disease) study,[28] for example, a possible benefit did not become apparent until after 2 years of treatment.

Conclusions

In summary, although the QE3 study shows that CoQ10 can be safely administered to patients with early PD at dosages of 1200 and 2400 mg/d, no therapeutic efficacy was demonstrated. In view of these results, we cannot recommend CoQ10 for the treatment of early PD.

ARTICLE INFORMATION

†Deceased.

Accepted for Publication: January 30, 2014.

Published Online: March 24, 2014. doi:10.1001/jamaneurol.2014.131.

The Parkinson Study Group QE3 Investigators/Authors: M. Flint Beal, MD; David Oakes, PhD; Ira Shoulson, MD; Claire Henchcliffe, MD; Wendy R. Galpern, MD, PhD; Richard Haas, MD; Jorge L. Juncos, MD; John G. Nutt, MD; Tiffini Smith Voss, MD; Bernard Ravina, MD, MSCE; Clifford M. Shults, MD; Karen Helles, MS, NP, CCRA; Victoria Snively, CCRC; Mark F. Lew, MD; Brian Griebner, BA, MBA; Arthur Watts, BS; Shan Gao, MS; Emmanuelle Pourcher, MD; Louisette Bond, RN; Katie Kompoliti, MD; Pinky Agarwal, MD; Cherissa Sia, MD; Mandar Jog, MD; Linda Cole, RN; Munira Sultana, MD; Roger Kurlan, MD; Irene Richard, MD; Cheryl Deeley, MS, RNC; Cheryl H. Waters, MD; Angel Figueroa, CCRC; Ani Arkun; Matthew Brodsky, MD; William G. Ondo, MD; Christine B. Hunter, RN, CCRC; Joohi Jimenez-Shahed, MD; Alicia Palao, MA; Janis M. Miyasaki, MD; Julie So; James Tetrud, MD; Liza Reys, CCRP; Katharine Smith, RN; Carlos Singer, MD; Anita Blenke; David S. Russell, MD, PhD; Candace Cotto, RN; Joseph H. Friedman, MD; Margaret Lannon, RN, MS; Lin Zhang, MD, PhD; Edward Drasby, MD; Rajeev Kumar, MD; Thyagarajan Subramanian, MD; Donna Stuppy Ford, LPN; David A. Grimes, MD; Diane Cote, RN; Jennifer Conway, RN; Andrew D. Siderowf, MD; Marian Leslie Evatt, MD; Barbara Sommerfeld, MSN; Abraham N. Lieberman, MD; Michael S. Okun, MD; Ramon L. Rodriguez, MD; Stacy Merritt, MA; Camille Louise Swartz, BA; W. R. Wayne Martin, MD; Pamela King, BSN, RN; Natividad Stover, MD; Stephanie Guthrie; Ray L. Watts, BS; Anwar Ahmed, MD; Hubert H. Fernandez, MD; Adrienna Winters, BS; Zoltan Mari, MD; Ted M. Dawson, MD, PhD; Becky Dunlop, RN; Andrew S. Feigin, MD; Barbara Shannon, RN; Melissa Jill Nirenberg, MD, PhD; Mattson Ogg, BA; Samuel A. Ellias, MD, PhD; Cathi-Ann Thomas, RN, MS; Karen Frei, MD; Ivan Bodis-Wollner, MD, DSc; Sofya Glazman, MD; Thomas Mayer, PsyD; Robert A. Hauser, MD, MBA; Rajesh Pahwa, MD; April Langhammer; Ranjit Ranawaya, MD; Lorelei Derwent, RN; Kapil D. Sethi, MD; Buff Farrow, BS, ED; Rajan Prakash, MD, MPH; Irene Litvan, MD; Annette Robinson, RN, BSN; Alok Sahay, MD; Maureen Gartner, RN; Vanessa K. Hinson, MD, PhD; Samuel Markind, MD; Melisa Pelikan, RN; Joel S. Perlmutter, MD; Johanna Hartlein; Eric Molho, MD; Sharon Evans, LPN; Charles H. Adler, MD, PhD; Amy Duffy, CRC; Marlene Lind, RN; Lawrence Elmer, MD, PhD; Kathy Davis, RN; Julia Spears, CCRC; Stephanie Wilson, RN, MSN; Maureen A. Leehey, MD; Neal Hermanowicz, MD; Shari Niswonger, RN; Holly A. Shill, MD; Sanja Obradov, BA; Alex Rajput, MD; Marilyn Cowper, BSc, Adv; Stephanie Lessig, MD; David Song, MD; Deborah Fontaine, RNCS, MS; Cindy Zadikoff, MD; Karen Williams; Karen A. Blindauer, MD; Jo Bergholte, BS, MS; Clara Schindler Propsom; Mark A. Stacy, MD; Joanne Field, BSN, RN; Dragos Mihaila, MD; Mark Chilton; Ergun Y. Uc, MD; Jeri Sieren, RN; David K. Simon, MD, PhD; Lauren Kraics; Althea Silver, MPH, BSN, RN; James T. Boyd, MD; Robert W. Hamill, MD; Christopher Ingvoldstad, BA; Jennifer Young, CCRP; Karen Thomas, DO; Sandra K. Kostyk, MD, PhD; Joanne Wojcieszek, MD; Ronald F. Pfeiffer, MD; Michel Panisset, MD; Monica Beland, RN; Stephen G. Reich, MD; Michelle Cines, RN; Nancy Zappala; Jean Rivest, MD; Richard Zweig, MD; L. Pepper Lumina; Colette Lynn Hilliard, MS; Stephen Grill, MD, PhD; Marye Kellermann, RN; Paul Tuite, MD; Susan Rolandelli, RN; Un Jung Kang, MD; Joan Young, CCRC; Jayaraman Rao, MD; Maureen M. Cook, RN, BSN; Lawrence Severt, MD; Karyn Boyar, RN, CNS, FNP.

Affiliations of The Parkinson Study Group QE3 Investigators/Authors: Department of Neurology, Weill Cornell Medical College, New York Hospital, New York (Beal, Henchcliffe, Arkun, Ogg); Department of Biostatistics, University of Rochester Medical Center, Rochester, New York (Oakes, Helles, Snively, Griebner, A. Watts, Gao); Department of Neurology, Georgetown University, Washington, DC (Shoulson); National Institutes of Health, Bethesda, Maryland (Galpern); Department of Neurosciences, University of California, San Diego, La Jolla (Haas, Shults, Litvan); Department of Neurology, Emory University School of Medicine, Wesley Woods Center, Atlanta, Georgia (Juncos, Evatt, Sommerfeld); Department of Neurology, Oregon Health and Science University, Portland (Nutt, Brodsky); Merck, New Jersey (Voss); Biogen Idec, Cambridge, Massachusetts (Ravina); VA Medical Center, San Diego, California (Shults); Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles (Lew); Department of Neurology, University of Rochester, Rochester, New York (A. Watts, Richard, Deeley); Québec Memory and Motor Skills Disorders Research Center, Clinique Sainte-Anne, Québec, Canada (Pourcher, Bond); Rush University Medical Center, Chicago, Illinois (Kompoliti); Booth Gardner Parkinson's Care Center, EvergreenHealth, Kirkland, Washington (Agarwal, Sia); London Health Sciences Centre, London, Ontario, Canada (Jog, Cole, Sultana); Overlook Medical Center, Atlantic Neuroscience Institute, Summit, New Jersey (Kurlan); Columbia University Medical Center, Neurological Institute, New York, New York (Waters, Figueroa); Department of Neurology, University of Texas Health Science Center at Houston (Ondo); Department of Neurology, Baylor College of Medicine, Houston, Texas (Hunter, Jimenez-Shahed, Palao); Morton and Gloria Shulman Movement Disorders Centre, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada (Miyasaki, So); The Parkinson's Institute and Clinical Center, Sunnyvale, California (Tetrud, Reys, Smith); Department of Neurology, University of Miami School of Medicine, Miami, Florida (Singer, Blenke); Institute for Neurodegenerative Disorders, New Haven, Connecticut (Russell, Cotto); Department of Neurology, Butler Hospital, Providence, Rhode Island (Friedman, Lannon); Alpert Medical School, Brown University, Providence, Rhode Island (Friedman); Port City Neurology, Inc, Scarborough, Maine (Lannon, Drasby); Department of Neurology, University of California, Davis, School of Medicine and Sacramento VA Medical Center, Sacramento (Zhang); Colorado Neurological Institute, Englewood (Kumar); Milton S. Hershey Medical Center, Department of Neurology, Pennsylvania State Hershey College of Medicine, Hershey (Subramanian, Ford); Ottawa Hospital Civic Site, Ottawa, Ontario, Canada (Grimes, Cote, Conway); Avid Radiopharmaceuticals, Philadelphia, Pennsylvania (Siderowf); Atlanta VA Medical Center, Atlanta, Georgia (Evatt); Muhammad Ali Parkinson Center, Barrow Neurological Institute, St Joseph's Hospital and Medical Center, Phoenix, Arizona (Lieberman); Department of Neurology, University of Florida Center for Movement Disorders and Neurorestoration, Gainesville (Okun, Rodriguez, Merritt, Swartz); Glenrose Rehabilitation Hospital, University of Alberta, Edmonton, Alberta, Canada (Martin, King); Department of Neurology, University of Alabama at Birmingham (Stover, Guthrie, R. L. Watts); Center for Neurological Restoration, Department of Neurology, Cleveland Clinic, Cleveland, Ohio (Ahmed, Fernandez, Winters); Department of Neurology, Johns Hopkins University, Baltimore, Maryland (Mari, Dawson, Dunlop, Grill); Feinstein Institute for Medical Research, Center for Neurosciences, Manhasset, New York (Feigin, Shannon); Department of Neurology, New York University Langone Medical Center, New York (Nirenberg); Department of

Neurology, Boston University School of Medicine, Boston, Massachusetts (Ellias, C. Thomas); The Parkinson's and Movement Disorder Institute, Fountain Valley, California (Frei); State University of New York, Downstate Medical Center, Brooklyn, New York (Bodis-Wollner, Glazman, Mayer); Department of Neurology, University of South Florida, Tampa (Hauser); Department of Neurology, University of Kansas Medical Center, Kansas City (Pahwa, Langhammer); Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada (Ranawaya, Derwent); Department of Neurology, Georgia Health Science University, Augusta (Sethi, Farrow, Prakash); Department of Neurology, University of Louisville, Kentucky (Robinson); University of Cincinnati College of Medicine, Cincinnati, Ohio (Sahay, Gartner); Department of Neurology, Medical University of South Carolina, Charleston (Hinson); Associated Neurologists, PC, Danbury, Connecticut (Markind, Pelikan); Department of Neurology, Washington University in St Louis, Missouri (Perlmutter, Hartlein); Movement Disorders Center, Albany Medical Center, Albany, New York (Molho, Evans); Parkinson's Disease and Movement Disorders Center, Department of Neurology, Mayo Clinic, Scottsdale, Arizona (Adler, Duffy, Lind); Center for Neurological Health, University of Toledo, Toledo, Ohio (Elmer); Department of Neurology, Medical University of Ohio at Toledo (Davis, Spears, Wilson); Department of Neurology, University of Colorado Health Science Center, Denver (Leehey); Department of Neurology, University of California, Irvine Medical Center, Irvine (Hermanowicz, Niswonger); Banner Sun Health Research Institute, Sun City, Arizona (Shill, Obradov); Department of Neurology, University of Saskatchewan, Royal University Hospital, Saskatchewan, Canada (Rajput, Cowper); Department of Neurology, University of California, San Diego, La Jolla (Lessig, Song, Fontaine); Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Zadikoff, Williams); Department of Neurology, Medical College of Wisconsin, Milwaukee (Blindauer, Bergholte, Propsom); Department of Neurology, Duke University, Durham, North Carolina (Stacy, Field); State University of New York Upstate Medical Center and Syracuse VA Medical Center, Syracuse (Mihaila, Chilton); Department of Neurology, University of Iowa, Iowa City (Uc, Sieren); Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts (Simon, Kraics, Silver); Department of Neurology, University of Vermont College of Medicine, Burlington (Boyd, Hamill, Ingvoldstad, J. Young); Department of Neurology, Ohio State University, Columbus (K. Thomas, Kostyk); Department of Neurology, Indiana University School of Medicine, Indianapolis (Wojcieszek); Department of Neurology, University of Tennessee Health Science Center, Memphis (Pfeiffer); Department of Neurology, CHUM–Hôpital Notre-Dame, Montréal, Québec, Canada (Panisset, Beland); Department of Neurology, University of Maryland School of Science, Baltimore (Reich, Cines, Zappala); Department of Neurology, University of Sherbrooke, Québec, Canada (Rivest); Department of Neurology, Louisiana State University Health Science Center, Shreveport (Zweig, Lumina); Lewis Hall Singletary Oncology Center, Thomasville, Georgia (Hilliard); Parkinson and Movement Disorders Center of Maryland, Elkridge (Kellermann); Department of Neurology, University of Minnesota, Minneapolis (Tuite, Rolandelli); Department of Neurology, University of Chicago, Chicago, Illinois (Kang, J. Young); Department of Neurology, Ochsner Clinic Foundation, New Orleans, Louisiana (Rao, Cook); Department of Neurology, Beth Israel Medical Center, New York, New York (Severt, Boyar).

Author Contributions: Drs Oakes and Beal had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Beal, Oakes, Shoulson, Henchcliffe, Galpern, Haas, Juncos, Nutt, Voss, Ravina.
Acquisition of data: Beal, Henchcliffe, Ravina, Helles, Snively, Lew, Griebner, A. Watts, Pourcher, Bond, Kompoliti, Agarwal, Sia, Jog, Cole, Sultana, Kurlan, Richard, Deeley, Waters, Figueroa, Arkun, Brodsky, Ondo, Hunter, Jimenez-Shahed, Palao, Miyasaki, So, Tetrud, Reys, Smith, Singer, Blenke, Russell, Cotto, Friedman, Lannon, Zhang, Drasby, Kumar, Subramanian, Stuppy Ford, Grimes, Cote, Conway, Siderowf, Evatt, Sommerfeld, Lieberman, Okun, Rodriguez, Merritt, Swartz, Martin, King, Stover, Guthrie, R. L. Watts, Ahmed, Fernandez, Winters, Mari, Dawson, Dunlop, Feigin, Shannon, Nirenberg, Ogg, Ellias, C.-A. Thomas, Frei, Bodis-Wollner, Glazman, Mayer, Hauser, Pahwa, Langhammer, Ranawaya, Derwent, Sethi, Farrow, Prakash, Litvan, Robinson, Sahay, Gartner, Hinson, Markind, Pelikan, Perlmutter, Hartlein, Molho, Evans, Adler, Duffy, Lind, Elmer, Davis, Spears, Wilson, Leehey, Hermanowicz, Niswonger, Shill, Obradov, Rajput, Cowper, Lessig, Song, Fontaine, Zadikoff, Williams, Blindauer, Bergholte, Schindler Propsom, Stacy, Field, Mihaila, Chilton, Uc, Sieren, Simon, Kraics, Silver, Boyd, Hamill, Ingvoldstad, Jennifer Young, K. Thomas, Kostyk, Wojcieszek, Pfeiffer, Panisset, Beland, Reich, Cines, Zappala, Rivest, Zweig, Lumina, Hilliard, Grill, Kellermann, Tuite, Rolandelli, Kang, Joan Young, Rao, Cook, Severt.
Analysis and interpretation of data: Beal, Oakes, Shoulson, Henchcliffe, Galpern, Haas, Juncos, Nutt, Voss, Ravina, Shults, Gao.
Drafting of the manuscript: Beal, Oakes, Shoulson, Henchcliffe, Galpern, Haas, Juncos, Nutt, Voss, Jog.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Oakes, Gao.
Obtained funding: Beal, Oakes, Shoulson.
Administrative, technical, and material support: Beal, Helles, Snively, Griebner, A. Watts, Bond, Sia, Cole, Sultana, Arkun, Palao, Tetrud, Reys, Blenke, Cotto, Friedman, Zhang, Kumar, Cote, Evatt, Rodriguez, King, Stover, Feigin, Shannon, Glazman, Sethi, Farrow, Gartner, Pelikan, Hartlein, Hermanowicz, Song, Williams, Field, Chilton, Hamill, Jennifer Young, Panisset, Cines, Zappala, Lumina, Tuite, Rao, Cook, Severt, Boyar.
Study supervision: Beal, Oakes, Shoulson, Henchcliffe, Galpern, Haas, Juncos, Nutt, Voss, Ravina, Jog, Hartlein.

Conflict of Interest Disclosures: None reported.

Funding/Support: The study was funded by grants from the National Institute of Neurological Disorders and Stroke to the Cornell University (U01 NS 050324; Dr Beal, PI) and to the University of Rochester (U01 NS050573; Dr Oakes, PI). We were also supported by the Parkinson's Disease Foundation with regard to facilitating minority enrollment.

Role of the Sponsor: Under the terms of the U01 funding mechanism, the steering committee included a National Institute of Neurological Disorders and Stroke representative (Dr Galpern), and the sponsor determined the charge to and membership of the DSMB, and approved all major protocol changes and the publication of this report.

The Parkinson Study Group QE3 steering committee: David Oakes, PhD (PI); M. Flint Beal, MD (PI); Ira Shoulson, MD (co-PI), Wendy R. Galpern, MD, PhD; Richard Haas, MD; Claire Henchcliffe, MD, DPhil; Jorge L. Juncos, MD; John Nutt, MD; Bernard Ravina, MD, MSCE; Tiffini Voss, MD; and Clifford Shults, MD (co-PI, deceased).

The Parkinson Study Group QE3 writing committee: Steering Committee and Emmanuelle Pourcher, MD; Pinky Agarwal, MD; Katie Kompoliti, MD; and Mandar Jog, MD.

Participating Sites (investigators and coordinators): *Clinique Sainte-Anne "Memoire et Mouvement"*: Emmanuelle Pourcher, MD; Louisette Bond, RN; *Rush University Medical Center*: Katie Kompoliti, MD; *Booth Gardner Parkinson's Care Center*: Pinky Agarwal, MD; Cherissa Sia, MD; *London Health Sciences Centre*: Mandar Jog, MD; Linda Cole, RN; Munira Sultana, MD; *University of Rochester*: Roger Kurlan, MD; Irene Richard, MD; Cheryl Deeley, MS, RNC; *Columbia University Medical Center*: Cheryl Waters, MD; Angel Figueroa, CCRC; Ani Arkun; *Oregon Health and Science University*: Matthew Brodsky, MD; *Baylor College of Medicine*: William Ondo, MD; Christine Hunter, RN, CCRC; Joohi Jimenez-Shahed, MD; Alicia Palao, MA; *Toronto Western Hospital, University Health Network*: Janis Miyasaki, MD; Julie So; *The Parkinson's Institute*: James Tetrud, MD; Liza Reys, CCRP; Katharine Smith, RN; *University of Miami*: Carlos Singer, MD; Anita Blenke; *Institute for Neurodegenerative Disorders*: David Russell, MD, PhD; Candace Cotto, RN; *Butler Hospital*: Joseph Friedman, MD; Margaret Lannon, RN, MS; *University of California, Davis, Medical Center*: Lin Zhang, MD, PhD; *Port City Neurology, Inc*: Edward Drasby, MD; Margaret Lannon, RN, MS; *Colorado Neurological Institute*: Rajeev Kumar, MD; *Milton S. Hershey Medical Center*: Thyagarajan Subramanian, MD; Donna Stuppy Ford, LPN; *Ottawa Hospital Civic Site*: David Grimes, MD; Diane Cote, RN; Jennifer Conway, RN; *University of Pennsylvania*: Andrew Siderowf, MD; *Emory University School of Medicine*: Marian Evatt, MD; Barbara Sommerfeld, MSN; *Barrow Neurological Institute*: Abraham Lieberman, MD; *University of Florida*: Michael S. Okun, MD; Ramon Rodriguez, MD; Stacy Merritt, MA; Camille Swartz, BA; *University of Alberta*: Wayne Martin, MD; Pamela King, BSN, RN; *University of Alabama at Birmingham*: Natividad Stover, MD; Stephanie Guthrie; Ray Watts; *Cleveland Clinic*: Anwar Ahmed, MD; Hubert Fernandez, MD; Adrienna Winters, BS; *Johns Hopkins University*: Zoltan Mari, MD; Ted Dawson, MD, PhD; Becky Dunlop, RN; *North Shore–LIJ Health System*: Andrew Feigin, MD; Barbara Shannon, RN; *Weill Medical College of Cornell University*: Melissa J. Nirenberg, MD, PhD; Mattson Ogg, BA; *Boston University*: Samuel Ellias, MD, PhD; Cathi-Ann Thomas, RN, MS; *The Parkinson's and Movement Disorder Institute*: Karen Frei, MD; *State University of New York Downstate Medical Center*: Ivan Bodis-Wollner, MD, DSc; Sofya

Glazman, MD; Thomas Mayer, PsyD; *University of South Florida*: Robert A. Hauser, MD, MBA; *University of Kansas Medical Center*: Rajesh Pahwa, MD; April Langhammer; *University of Calgary*: Ranjit Ranawaya, MD; Lorelei Derwent, RN; *Georgia Health Science University*: Kapil Sethi, MD; Buff Farrow, BS, ED; Rajan Prakash, MD, MPH; *University of Louisville*: Irene Litvan, MD; Annette Robinson, RN, BSN; *University of Cincinnati/ Cincinnati Children's Hospital*: Alok Sahay, MD; Maureen Gartner, RN; *Medical University of South Carolina*: Vanessa Hinson, MD, PhD; *Associated Neurologists, PC*: Samuel Markind, MD; Melisa Pelikan, RN; *Washington University*: Joel S. Perlmutter, MD; Johanna Hartlein; *Albany Medical Center*: Eric Molho, MD; Sharon Evans, LPN; *Mayo Clinic Arizona*: Charles Adler, MD, PhD; Amy Duffy, CRC; Marlene Lind, RN; *Medical University of Ohio*: Lawrence Elmer, MD, PhD; Kathy Davis, RN; Julia Spears, CCRC; Stephanie Wilson, RN, MSN; *University of Colorado Denver*: Maureen Leehey, MD; *University of California, Irvine*: Neal Hermanowicz, MD; Shari Niswonger, RN; *Banner Research Institute*: Holly Shill, MD; Sanja Obradov, BA; *Saskatoon District Health Board Royal University Hospital*: Alexander Rajput, MD; Marilyn Cowper, BSc, Adv; *University of California, San Diego*: Stephanie Lessig, MD; David Song, MD; Deborah Fontaine, RNCS, MS; *Northwestern University*: Cindy Zadikoff, MD; Karen Williams; *Medical College of Wisconsin*: Karen Blindauer, MD; Jo Bergholte, BS, MS; Clara Schindler Propsom; *Duke University*: Mark Stacy, MD; Joanne Field, BSN, RN; *State University of New York Upstate Medical Center and Syracuse VA Medical Center*: Dragos Mihaila, MD; Mark Chilton; *University of Iowa*: Ergun Uc, MD; Jeri Sieren, RN; *Beth Israel Deaconess Medical Center*: David K. Simon, MD, PhD; Lauren Kraics; Althea Silver, MPH, BSN, RN; *University of Vermont*: James Boyd, MD; Robert Hamill, MD; Christopher Ingvoldstad, BA; Jennifer Young, CCRP; *Ohio State University*: Karen Thomas, DO; Sandra Kostyk, MD, PhD; *Indiana University School of Medicine*: Joanne Wojcieszek, MD; *University of Tennessee Health Science Center*: Ronald F. Pfeiffer, MD; *CHUM–Hôpital Notre-Dame*: Michel Panisset, MD; Monica Beland, RN; *University of Maryland School of Medicine*: Stephen Reich, MD; Michelle Cines, RN; Nancy Zappala; *University of Sherbrooke*: Jean Rivest, MD; *Louisiana State University Health Science Center Shreveport*: Richard Zweig, MD; L. Pepper Lumina; Colette Hilliard, MS; *Parkinson and Movement Disorders Center of Maryland*: Stephen Grill, MD, PhD; Marye Kellermann, RN; *University of Minnesota*: Paul Tuite, MD; Susan Rolandelli, RN; *University of Chicago*: Un Jung Kang, MD; Joan Young, CCRC; *Ochsner Clinic Foundation*: Jayaraman Rao, MD; Maureen Cook, RN, BSN; *Beth Israel Medical Center*: W. Lawrence Severt, MD; Karyn Boyar, RN, CNS, FNP.

Biostatistics/Coordination Center: David Oakes, PhD; Michael McDermott, PhD; Arthur Watts, BS; Shan Gao, MS; Brian Griebner, BA, MBA; Karen Helles, MS, NP, CCRA; Sandra Plumb, BS; and Victoria Snively, CCRC.

Medical Monitor: Mark Lew, MD; Tiffini Voss, MD.

Data and Safety Monitoring Committee: Cynthia Gross, PhD; Roger Albin, MD; Karen L. Bell, MD; Donna T. Chen, MD, MPH; and David E. Levy, MD.

Coordination Center: Amy Beimler, Rory Doolan, Sue Henderson, Lisa Lang, Gina Lau, Nichole McMullen, and Karen Rothenburgh.

Disclaimer: Dr Shoulson is the Clinical Trials Editor for *JAMA Neurology* and was not involved in the editorial review of the manuscript.

Additional Contributions: We thank the following QE3 investigators and coordinators who worked on the study from time of first enrollment. Arita McCoy (Johns Hopkins University); Bari J. Dorward (Booth Gardner Parkinson's Care Center); Michelle Tran and Jassie Sombai (The Parkinson's and Movement Disorder Institute); Monica Quesada (University of Miami); Roxana Hupcey (University of California, Davis Medical Center); Dawn Miracle (Colorado Neurological Institute); Lisa Altin (University of Pennsylvania); Mary Louise Weeks (Emory University School of Medicine); Edith Simpson (Barrow Neurological Institute); Michele Suelter (University of Florida); Ingrid Scott (University of Alberta); Rebecca McMurray (University of Alabama at Birmingham); Malinka Velcheva (Weill Medical College of Cornell University); Theresa McClain and Leyla Khavarian (University of South Florida); Jennifer Zimmerman (Medical University of South Carolina); Marci Zomok (Mayo Clinic Arizona); Mary E. Scott (Medical University of Ohio); Heena Olalde (University of Iowa); Jared Miller (Beth Israel Deaconess Medical Center); Colette Oesterle (University of Vermont); Paige Pancake (Ohio State University); Joann Belden (Indiana University School of Medicine); Daniel Soucy (University of Sherbrooke); Labrillia Johnson (Louisiana State University Health Science Center Shreveport); Rabih Kashouty and Lauren Roth (Beth Israel Medical Center); Lisa Niles, MS (Butler Hospital); and Breanna Nickels (Colorado Neurological Institute). These investigators and coordinators were compensated for their work in this study. The investigators served as individual site directors and performed the primary neurologic assessments. The site coordinators worked with their investigator and the coordination center staff to perform tasks designated to them by the study protocol and operations manual.

REFERENCES

1. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*. 2007;68(5):384-386.

2. Thomas B, Beal MF. Mitochondrial therapies for Parkinson's disease. *Mov Disord*. 2010;25(suppl 1):S155-S160.

3. Beal MF. Therapeutic approaches to mitochondrial dysfunction in Parkinson's disease. *Parkinsonism Relat Disord*. 2009;15(suppl 3):S189-S194.

4. Burchell VS, Gandhi S, Deas E, Wood NW, Abramov AY, Plun-Favreau H. Targeting mitochondrial dysfunction in neurodegenerative disease: part I. *Expert Opin Ther Targets*. 2010;14(4):369-385.

5. Shults CW. Therapeutic role of coenzyme Q(10) in Parkinson's disease. *Pharmacol Ther*. 2005;107(1):120-130.

6. Shults CW, Haas RH, Passov D, Beal MF. Coenzyme Q10 levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects. *Ann Neurol*. 1997;42(2):261-264.

7. Spindler M, Beal MF, Henchcliffe C. Coenzyme Q10 effects in neurodegenerative disease. *Neuropsychiatr Dis Treat*. 2009;5:597-610.

8. Koroshetz WJ, Jenkins BG, Rosen BR, Beal MF. Energy metabolism defects in Huntington's disease and effects of coenzyme Q10. *Ann Neurol*. 1997;41(2):160-165.

9. Cooper JM, Korlipara LV, Hart PE, Bradley JL, Schapira AH. Coenzyme Q10 and vitamin E deficiency in Friedreich's ataxia: predictor of efficacy of vitamin E and coenzyme Q10 therapy. *Eur J Neurol*. 2008;15(12):1371-1379.

10. Stamelou M, Reuss A, Pilatus U, et al. Short-term effects of coenzyme Q10 in progressive supranuclear palsy: a randomized, placebo-controlled trial. *Mov Disord*. 2008;23(7):942-949.

11. Shults CW, Oakes D, Kieburtz K, et al; Parkinson Study Group. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol*. 2002;59(10):1541-1550.

12. Storch A, Jost WH, Vieregge P, et al; German Coenzyme Q(10) Study Group. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q(10) in Parkinson disease. *Arch Neurol*. 2007;64(7):938-944.

13. Fahn S, Elton R; Members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. *Recent Developments in Parkinson's Disease*. Vol 2. Florham Park, NJ: Macmillan Healthcare Information;1987:153-163.

14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.

15. Parkinson Study Group PRECEPT Investigators. Mixed lineage kinase inhibitor CEP-1347 fails to delay disability in early Parkinson disease. *Neurology*. 2007;69(15):1480-1490.

16. Shults CW, Flint Beal M, Song D, Fontaine D. Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. *Exp Neurol*. 2004;188(2):491-494.

17. NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. *Neurology*. 2007;68(1):20-28.

18. Snow BJ, Rolfe FL, Lockhart MM, et al; Protect Study Group. A double-blind, placebo-controlled study to assess the mitochondria-targeted antioxidant MitoQ as a disease-modifying therapy in Parkinson's disease. *Mov Disord*. 2010;25(11):1670-1674.

19. Schapira AH, Gegg M. Mitochondrial contribution to Parkinson's disease pathogenesis. *Parkinsons Dis*. 2011;2011:159160.

20. Henchcliffe C, Beal MF. Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. *Nat Clin Pract Neurol*. 2008;4(11):600-609.

21. Franke AA, Morrison CM, Bakke JL, Custer LJ, Li X, Cooney RV. Coenzyme Q10 in human blood: native levels and determinants of oxidation during processing and storage. *Free Radic Biol Med*. 2010;48(12):1610-1617.

22. Bhagavan HN, Chopra RK. Plasma coenzyme Q10 response to oral ingestion of coenzyme Q10 formulations. *Mitochondrion*. 2007;7(suppl):S78-S88.

23. Littarru GP, Langsjoen P. Coenzyme Q10 and statins: biochemical and clinical implications. *Mitochondrion*. 2007;7(suppl):S168-S174.

24. Wang XL, Rainwater DL, Mahaney MC, Stocker R. Cosupplementation with vitamin E and coenzyme Q10 reduces circulating markers of inflammation in baboons. *Am J Clin Nutr*. 2004;80(3):649-655.

25. McDonald SR, Sohal RS, Forster MJ. Concurrent administration of coenzyme Q10 and alpha-tocopherol improves learning in aged mice. *Free Radic Biol Med*. 2005;38(6):729-736.

26. Maetzler W, Hausdorff JM. Motor signs in the prodromal phase of Parkinson's disease. *Mov Disord*. 2012;27(5):627-633.

27. Marras C, Lang AE, Eberly SW, et al; Parkinson Study Group DATATOP and PRECEPT investigators. A comparison of treatment thresholds in two large Parkinson's disease clinical trial cohorts. *Mov Disord*. 2009;24(16):2370-2378.

28. Huntington Study Group. A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. *Neurology*. 2001;57(3):397-404.