HIGH LIGHT
CME

A randomized clinical trial of coenzyme Q_{10} and GPI-1485 in early Parkinson disease

The NINDS NET-PD Investigators*

Abstract—*Objective:* To determine if future studies of coenzyme Q_{10} and GPI-1485 in Parkinson disease (PD) may be warranted. *Methods:* We conducted a randomized, double-blind, calibrated futility clinical trial of coenzyme Q10 and GPI-1485 in early untreated PD using placebo data from the DATATOP study to establish the futility threshold. *Results:* The primary outcome measure (change in total Unified Parkinson's Disease Rating Scale scores over 1 year) did not meet the prespecified criteria for futility for either agent. Secondary analyses using calibration controls and other more recent placebo data question the appropriateness of the predetermined definition of futility, and suggest that a more restrictive threshold may be needed. *Conclusions:* Coenzyme Q_{10} and GPI-1485 may warrant further study in Parkinson disease, although the data are inconsistent. Additional factors (cost, availability of other agents, more recent data on placebo outcomes, other ongoing trials) should also be considered in the selection of agents for Phase III studies.

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Preclinical and clinical investigators are actively seeking interventions that may delay or slow the progression of Parkinson disease (PD). The National Institute for Neurological Disorders and Stroke (NINDS) Committee to Identify Neuroprotective Agents in Parkinson's (CINAPS) attempted to systematically review compounds that may be potentially effective in this regard.[1] Two compounds that emerged from this review were coenzyme Q_{10} and GPI-1485.

Coenzyme Q_{10}, which is also known as ubiquinone, is an essential cofactor in the electron transport chain[2,3] and is a potent antioxidant in both mitochondria and lipid membranes.[4,5] There is evidence of mitochondrial dysfunction in PD,[6] reduced mitochondrial complex I activity in patients with PD,[7] as well as reduced levels of CoQ_{10} vs age-comparable controls.[8,9] There are promising results in preclinical and clinical studies of PD[10] and other neurodegenerative disorders, including Huntington disease.[11] CoQ_{10} is a widely used dietary supplement that appears safe and well tolerated in several different disease populations. A pilot study of CoQ_{10} in early untreated PD[12] (referred to as QE2) suggested that 1,200 mg daily may have a beneficial effect on disease progression. Subsequent pilot investigations have suggested that dosages as high as 2,400 mg may be well tolerated in individuals with PD and other neurodegenerative disorders.[13]

GPI-1485 is a novel neuroimmunophilin-ligand compound. Immunophilins are intracellular receptor proteins that bind to the immunosuppressive drugs cyclosporine A, FK506, and rapamycin.[14] The FK506-binding protein (FKBP) is an immunophilin that binds with high affinity to FK506 and rapamycin and may mediate some pharmacologic actions of these molecules. Immunophilin-binding proteins are enriched 10- to 50-fold more in the brain than in the immune system,[15] and immunosuppressive drugs that bind to immunophilin-binding proteins can promote nerve growth in vitro and in vivo[16-21] independent of their immunosuppressive actions. These neuroimmunophilin ligands are orally bioavailable. A 6-month double-blind, placebo-controlled phase II clinical trial of GPI-1485 (800 or 4,000 mg daily) in patients with mild to moderate PD showed this agent was well tolerated, with only a higher incidence of nausea and indigestion in those subjects taking the higher dosage.[22] There was a trend toward a favorable impact on imaging measures, although there were no clear benefits on clinical measures.

Based on the systematic review of previous studies of CoQ_{10} and GPI-1485, as well as their generally favorable tolerability profiles, CoQ_{10} and GPI-1485 were selected for inclusion in a futility study to determine whether it is worthwhile to evaluate the possible disease-modifying effects of these compounds in future phase III trials. Futility trials are phase II trials designed to eliminate agents that

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show low potential for further development by comparing the primary outcome measure of the treatment arm to a prespecified threshold value. The use of this type of phase II study in PD has previously been discussed in the evaluations of creatine and minocycline[23,24] (later referred to as the FS1 study).

Methods. *Organization.* This multicenter clinical trial was organized by the Clinical Trials Coordination Center (CTCC) at the University of Rochester, the Department of Biostatistics, Bioinformatics and Epidemiology at the Medical University of South Carolina, and NINDS, who sponsored the trial. The steering committee developed the protocol and consent forms with the participating sites and guided the implementation of the trial. The protocol and consent forms were approved by a NINDS–appointed oversight board (OSB), an independent data safety monitoring board (DSMB), and the institutional review boards (IRBs) of each of the participating sites. The DSMB monitored the safety, data integrity, and progress of the trial.

Participants. Participants were men and women aged 30 and over who had a diagnosis of PD but did not require any medications for the treatment of their symptoms at the time of study entry. Two of three cardinal manifestations of PD (tremor, rigidity, and bradykinesia) were required; these findings had to be asymmetric. The diagnosis of PD must have been made within 5 years of randomization. Women of childbearing potential were required to use adequate birth control and have a negative pregnancy test at baseline. Subjects were excluded if they had any secondary causes of parkinsonism, such as drug-induced parkinsonism or structural lesions; atypical parkinsonian syndromes; gait freezing or impairment in postural reflexes; prior stereotaxic surgery for PD; used GPI-1485 or CoQ_{10} or an investigational agent within 90 days prior to randomization; known hypersensitivity to CoQ_{10} or GPI-1485; or any clinically significant medical condition that could interfere with the subject's ability to safely participate in the study or to be followed.

Study design and randomization. A single arm futility study design was used to assess each of the study drugs, CoQ_{10} and GPI-1485. We included a placebo arm for calibration, to verify and update the historical control assumptions used in sample size estimation.[25] Eligible subjects were randomly assigned in a 1:1:1 fashion to receive 1) 2,400 mg of CoQ_{10} and placebo for GPI-1485, 2) placebo for CoQ_{10} and 4,000 mg of GPI-1485, or 3) placebo for CoQ_{10} and placebo for GPI-1485. The futility analysis was conducted at 12 months of follow-up. Subjects and investigators were kept blinded to treatment group. The statistical center generated the random allocations sequence, and the sites accessed the blinded treatment assignment via a secured Web page.

Study intervention. CoQ_{10} was administered as 600 mg chewable wafers. One wafer was taken four times daily. GPI-1485 was administered as 250 mg tablets with four tablets being taken four times daily. CoQ_{10} and matching placebo wafers were manufactured by and purchased in bulk from Enzymatic Therapy Inc. Both active and placebo formulations of CoQ_{10} contained 300 IU of vitamin E; thus all patients received a total daily dose of 1,200 IU vitamin E. GPI-1485 and matching placebo tablets were provided by Guilford Pharmaceuticals Inc.

Outcome measures. The primary, prespecified outcome measure was the change in the total Unified PD Rating Scale (UPDRS) score from baseline to either the time at which there was sufficient disability to warrant symptomatic therapy for PD or 12 months, whichever came first. Disability was assessed by the site investigator, based on impairment in ambulation, activities of daily living, and occupational status. Investigators were trained on this endpoint using case vignettes, and each decision to initiate therapy was retrospectively reviewed by members of the Steering Committee and the DSMB, although the site investigator had the final decision. The mean change in total UPDRS for each treatment group was compared to a prespecified futility threshold defined as a 30% reduction in the historically derived change in total UPDRS, which was based on the placebo arm of a previous clinical trial.[26]

Secondary outcome measures included comparisons to an updated estimate of the futility threshold based on the observed progression in the calibration placebo group, if this update was needed (see statistical analyses). Additional secondary outcome measures included changes from baseline in UPDRS subscores, Hoehn & Yahr stage, investigator-rated Schwab and England activities of daily living score, as well as tolerability defined as the proportion of subjects taking study drug for the full 12 months and number of serious adverse events (SAEs). All SAEs were reviewed by the study medical monitor and an independent medical monitor. Both the site investigator and the medical monitors assessed the potential relationship between SAEs and study drug, but remained blinded to treatment assignment.

Study procedures. At the screening visit, the purpose and potential risks and benefits were explained to potential subjects, and each subject provided written informed consent. Subjects had

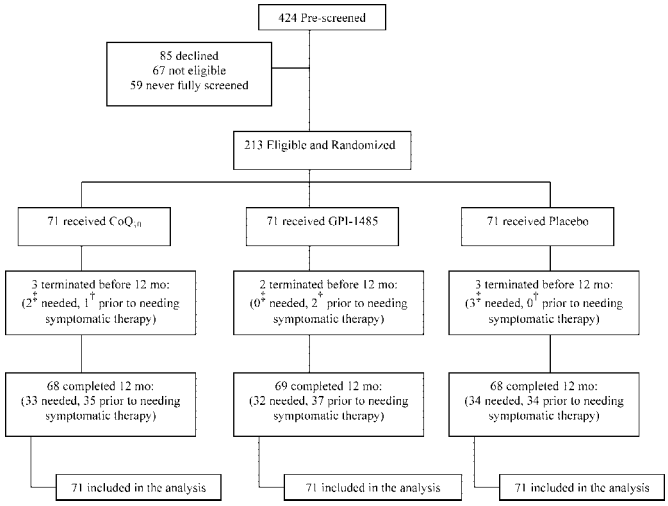

Figure 1. Flow diagram from screening to study completion (time until 12 months or need for symptomatic therapy, whatever comes first). ‡No imputation required. †Required imputation. One additional patient was imputed in the GPI-1485 arm due to missing data. Of the 424 prescreened, 213 were randomized into the trial, 85 declined (major reasons being not interested, travel requirements, or placebo), 50 were excluded prior to signing, and 17 were excluded after signing informed consent (major reasons being exclusionary medications or Parkinson disease was too advanced), and the remaining 59 were identified as potential subjects (via chart reviews) but never screened.

Table 1 *Baseline characteristics*

	CoQ_{10} (n = 71)	GPI-1485 (n = 71)	Placebo (n = 71)
Male, n (%)	43 (61)	46 (65)	50 (70)
Non-Hispanic white, n (%)	64 (90)	64 (90)	63 (89)
Hispanic, n (%)	2 (3)	4 (6)	2 (3)
Age, y (SD)	60.7 (9.9)	62.2 (10.6)	60.1 (10.6)
Duration PD, y	0.53 (0.78)	0.76 (0.94)	0.69 (0.89)
Total UPDRS	22.5 (8.97)	22.0 (8.46)	22.6 (9.22)
UPDRS Mental	0.93 (1.15)	1.15 (1.48)	0.77 (1.12)
UPDRS Motor	15.5 (6.60)	15.3 (6.18)	16.1 (6.87)
UPDRS ADL	6.01 (3.22)	5.52 (2.92)	5.73 (3.29)
Hoehn & Yahr	1.49 (0.56)	1.54 (0.53)	1.41 (0.50)
Schwab & England ADL	92.8 (5.52)	93.5 (4.96)	92.6 (4.77)

PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale; ADL = activities of daily living.

Table 2 *Primary outcome: Change in total Unified Parkinson's Disease Rating Scale from baseline to 12 months or need for symptomatic therapy (whichever comes first)*

			Primary analysis* (DATATOP)		Bayesian: DATATOP, FS1[23], and current study		Weighted mean: FS1[23], PRECEPT[41], and current study (without DATATOP)	
Treatment group	Mean (SD)	95% CI	t-Test for H_0: mean ≤7.46 vs H_A: mean >7.46	p Value	t-Test for H_0: mean ≤6.69 vs H_A: mean >6.69	p Value	t-Test for H_0: mean ≤4.96 vs H_A: mean >4.96	p Value
DATATOP placebo/tocopherol	10.65 (10.4)	(9.63, 11.67)						
CoQ_{10}	7.52 (8.87)	(5.42, 9.62)	0.06	0.48	0.79	0.22	2.43	0.01
GPI-1485	7.41 (8.83)	(5.32, 9.5)	−0.04	0.52	0.69	0.25	2.34	0.01
Current study placebo	6.31 (8.47)	(4.31, 8.31)						
Creatine[23]	5.6 (8.69)	(3.48, 7.72)	−1.7	0.96	−1.03	0.85	0.60	0.27
Minocycline[23]	7.09 (8.71)	(4.95, 9.23)	−0.34	0.63	0.37	0.36	1.99	0.03
Placebo[23]	8.39 (9.76)	(6.01, 10.8)						

Worst change score for the group was used to impute missing values. There was one missing value imputed in the CoQ_{10} group, three in GPI-1485, and zero in placebo.

* Primary analysis compares each treatment to the futility threshold of 7.46, or 70% of historical control. Secondary and exploratory analyses included 1) an updated futility threshold of 6.69 based on the historical control and the calibration groups, and 2) a futility threshold of 4.96 based on the calibration placebos and a more current placebo (PRECEPT).

a baseline medical history taken, a physical examination, and the UPDRS evaluation. Blood was obtained for serum chemistry and complete blood count, and urine was obtained for urinalysis, all of which were performed at a central laboratory (Covance Laboratories, Indianapolis, IN). Participants were re-evaluated at 1, 3, 6, 9, and 12 months (±6 days) after the baseline visit using a battery of clinical scales (UPDRS parts I–IV,[27] Hoehn and Yahr,[28] Schwab & England,[29] Geriatric Depression Scale,[30] Modified Rankin Scale,[31] Total Functional Capacity,[32] SF-12,[33] PDQ-39,[34] Repeatable Battery for the Assessment of Neuropsychological Status [RBANS],[35] Frontal Assessment Battery,[36] and Letter Number Sequencing[37]), and laboratory tests were repeated at 6 and 12 months.

Sample size and statistical analysis. The sample size estimation was based on data from patients receiving placebo or tocopherol participating in the Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism trial (DATATOP),[38] a large cohort of patients with newly diagnosed PD similar to the present study population. The DATATOP study met the Pocock criteria for the use of historical controls.[39] The observed mean change from baseline in the total UPDRS in placebo/tocopherol patients (13 months ± 30 days) was 10.65 (SD 10.4). The threshold value for futility

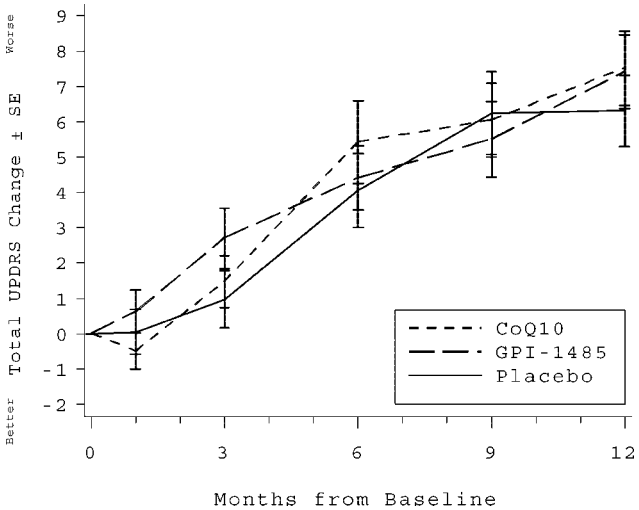

Figure 2. Change from baseline in total Unified Parkinson's Disease Rating Scale over time. Excludes visits conducted after patients needed symptomatic treatment, and carries forward the need for symptomatic therapy visit. Missing visits are imputed with worst change score for the group. Bars represent standard errors of the means at 1, 3, 6, 9, and 12 months.

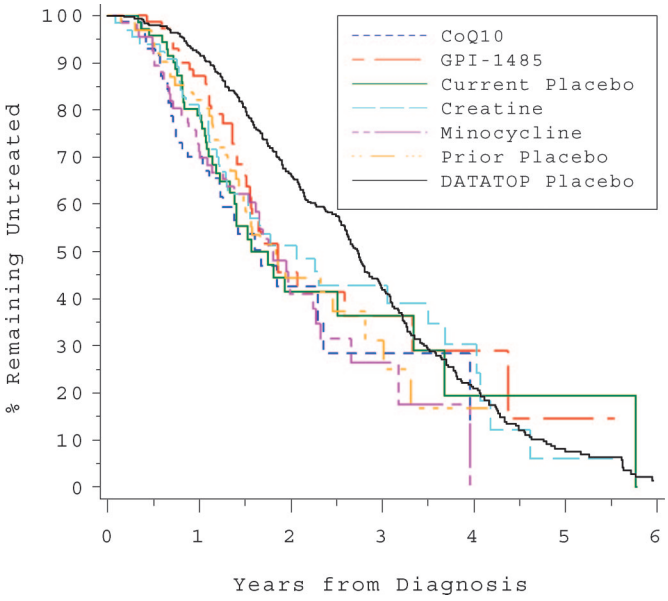

Figure 3. Kaplan-Meier curve of time from diagnosis to need for symptomatic therapy. DATATOP includes placebo and tocopherol arms.

Table 3 *Total Unified Parkinson's Disease Rating Scale (UPDRS) change from baseline to 12 months vs change from baseline to need for symptomatic therapy visit (for DATATOP control and NET-PD treatment arms)*

	Complete 12 mo without symptomatic treatment*		Require symptomatic treatment before 12 mo	
Treatment	N (%)	Mean change UPDRS (SD)	N (%)	Mean change UPDRS (SD)
DATATOP placebo/tocopherol, n = 401	265 (66)	7.68 (9.28)	136 (34)	16.4 (10.1)
CoQ_{10}, n = 71	36 (51)	6.44 (8.7)	35 (49)	8.63 (9.02)
GPI-1485, n = 71	39 (55)	4.31 (8.51)	32 (45)	11.2 (7.78)
Current study placebo, n = 71	34 (48)	3.35 (7.53)	37 (52)	9.03 (8.47)
Creatine,[23] n = 67	38 (57)	3.32 (8.40)	29 (43)	8.59 (8.27)
Minocycline,[23] n = 66	32 (48)	2.69 (7.41)	34 (52)	11.24 (7.84)
FS1 placebo,[23] n = 67	34 (51)	7.06 (10.07)	33 (49)	9.76 (9.40)

* Missing values imputed with worst change score for the group. There was one missing value imputed in the CoQ_{10} group, three in GPI-1485, zero in current study placebo, two in creatine, zero in minocycline, and three in FS1[23] placebo.

was defined as 30% less progression on the total UPDRS than the 10.65 unit change in DATATOP, or 7.46. A sample size of 58 per group provided power greater than 85% to reject the null hypothesis of non-futility if, in fact, the true mean total UPDRS worsening is significantly greater than the threshold of 7.46 at the design alternative of 10.65. As with most clinical studies, a certain degree of noncompliance (including subject withdrawal or loss to follow-up) was expected. Assuming the noncompliance rate to be minimal at 5%, the required sample size was increased to 65 subjects per treatment arm to account for the noncompliance in the intent-to-treat analysis.[40] For each study arm, the set of statistical hypotheses tested was as follows: H_0: $\Delta_i \leq 7.46$ vs H_A: $\Delta_i > 7.46$, where Δ_i is the mean change score (total UPDRS at 12 months or at the time of initiation of symptomatic therapy − total UPDRS at baseline) for the ith treatment arm, and 7.46 was the maximum mean increase (worsening) in the score between baseline and 12 months sufficient to warrant further evaluation of the drug in a phase III trial. The hypothesis was tested with a one-sample t-test at one-sided alpha level of 0.10. If the null hypothesis was rejected ($p \leq 0.1$) then the drug would be considered futile for further testing in a phase III trial.

A secondary analysis of the primary outcome was planned if the mean change in the total UPDRS score observed in the calibration placebo group fell outside of the 95% CI of the historical control mean change score of 10.65 (±1.02). The historical rate derived from DATATOP would be updated by incorporating the information from the calibration placebo group using Bayesian methods to derive a posterior mean. The futility threshold would be recomputed as 70% of this posterior mean, and a one-sample t-test would be performed for each active treatment arm.

Analysis of the primary outcome was conducted under the intent-to-treat principle where all randomized subjects were included in the analyses. For the small proportion of subjects who were lost to follow-up, we imputed their UPDRS change scores using the worst change score observed within their respective treatment groups. An exploratory analysis included multiple imputations to account for missing values. Additional unplanned exploratory analyses were performed using the placebo group from a separate concurrent trial in early PD,[41] and such analyses were also applied to the data obtained from the previously conducted futility trials evaluating creatine and minocycline.[23] No two-sample comparisons were made between placebo and treatment groups as the study was not designed or powered for this type of analysis. A two-sample comparison would be underpowered compared to the planned futility analysis.

Table 4 *Secondary outcome measures: change from baseline to 12 months or need for symptomatic therapy (whichever came first)*

Outcome	Treatment group	Mean (SD)	95% CI
Motor UPDRS	CoQ_{10}	4.73 (6.66)	(3.16, 6.31)
	GPI-1485	5.34 (7.25)	(3.62, 7.05)
	Placebo	3.79 (6.16)	(2.33, 5.25)
Mental UPDRS	CoQ_{10}	0.68 (1.49)	(0.32, 1.03)
	GPI-1485	0.21 (1.51)	(−0.15, 0.57)
	Placebo	0.48 (1.18)	(0.2, 0.76)
ADL UPDRS	CoQ_{10}	2.15 (3.05)	(1.43, 2.88)
	GPI-1485	2.11 (2.47)	(1.53, 2.7)
	Placebo	2.04 (2.93)	(1.35, 2.74)
Hoehn & Yahr	CoQ_{10}	0.32 (0.65)	(0.17, 0.48)
	GPI-1485	0.21 (0.74)	(0.04, 0.39)
	Placebo	0.31 (0.65)	(0.16, 0.46)
Schwab & England (investigator)	CoQ_{10}	−5.5 (8.16)	(−7.4, −3.6)
	GPI-1485	−4.4 (6.32)	(−5.9, −2.9)
	Placebo	−4.9 (7.63)	(−6.7, −3.1)

ADL = activities of daily living; UPDRS = Unified Parkinson's Disease Rating Scale.

Table 5 *Adverse events occurring in more than 5% of subjects in any one treatment group*

Event (WHO term)	CoQ_{10}, no. of subjects (%)	GPI-1485, no. of subjects (%)	Placebo, no. of subjects (%)	Total no. of subjects (%)
Nausea	8 (11)	17 (24)	13 (18)	38 (18)
Joint pain	7 (10)	11 (15)	10 (14)	28 (13)
Upper respiratory tract infection	9 (13)	8 (11)	10 (14)	27 (13)
Headache	10 (14)	5 (7)	10 (14)	25 (12)
Anxiety	9 (13)	4 (6)	10 (14)	23 (11)
Diarrhea	5 (7)	10 (14)	6 (8)	21 (10)
Insomnia	6 (8)	8 (11)	5 (7)	19 (9)
Depression	8 (11)	4 (6)	6 (8)	18 (8)
Sinusitis	5 (7)	4 (6)	8 (11)	17 (8)
Fatigue	3 (4)	6 (8)	8 (11)	17 (8)
Edema	9 (13)	4 (6)	4 (6)	17 (8)
Coughing	4 (6)	5 (7)	5 (7)	14 (7)
Back pain	6 (8)	4 (6)	4 (6)	14 (7)
Constipation	6 (8)	5 (7)	2 (3)	13 (6)
Lightheaded feeling	6 (8)	4 (6)	4 (6)	14 (7)
Heartburn	4 (6)	5 (7)	2 (3)	11 (5)
Fall	4 (6)	1 (1)	5 (7)	10 (5)
Dizziness	3 (4)	0 (0)	6 (8)	9 (4)
Appetite decreased	1 (1)	4 (6)	3 (4)	8 (4)
Gastroesophageal reflux	5 (7)	0 (0)	3 (4)	8 (4)
Urinary frequency	3 (4)	6 (8)	1 (1)	10 (5)
Throat sore	4 (6)	1 (1)	3 (4)	8 (4)
Hypercholesterolemia	1 (1)	2 (3)	4 (6)	7 (3)
Bruise	2 (3)	0 (0)	5 (7)	7 (3)
Urinary urgency	2 (3)	4 (6)	1 (1)	7 (3)
Influenza-like symptoms	4 (6)	1 (1)	2 (3)	7 (3)
Rash	2 (3)	1 (1)	4 (6)	7 (3)
Arthritis	0 (0)	4 (6)	2 (3)	6 (3)
Tremor	1 (1)	0 (0)	4 (6)	5 (2)
Dental carries	0 (0)	4 (6)	0 (0)	4 (2)

Results. *Subjects enrolled.* Between March and July of 2004, 424 potential subjects were identified and evaluated for trial eligibility. Of these, 213 subjects met study entry criteria and were randomized equally to one of three treatment groups (figure 1). The groups were similar at baseline on demographic variables, total UPDRS, and UPDRS subscores (table 1).

Futility. There were few missed visits with only three subjects in the GPI-1485 arm, one subject in the CoQ_{10} arm, and no controls having missing values requiring imputation. The mean change (SD) in total UPDRS score from either baseline to 12 months or the time at which symptomatic therapy was needed was 7.52 (8.87) for the CoQ_{10} group and 7.41 (8.83) for the GPI-1485 group (table 2, figure 2). The null hypothesis that the means were significantly less than or equal to the threshold value of 7.46 (30% less than the 10.65 DATATOP historical rate of progression) could not be rejected for CoQ_{10} ($p = 0.48$) or GPI-1485 ($p = 0.52$). Hence, CoQ_{10} and GPI-1485 could not be rejected as futile using this analysis and, therefore, met the criteria for consideration for further clinical testing. Using multiple imputation instead of worst change score for the group to account for missing observations yielded similar results.

The calibration placebo group mean change of 6.31 (8.47) fell outside the 95% CI for the DATATOP historical control of 9.63 to 11.67. As planned in the initial study design, the historical control rate was updated using the observed placebo information and the placebo information from the previous similarly designed futility study.[23] With this update the threshold value for futility decreased from 7.46 to 6.69. Against this comparison value, neither CoQ_{10} ($p = 0.22$) or GPI-1485 ($p = 0.25$) could be rejected as futile.

Based on data from the futility study of CoQ_{10} and GPI-1485, as well as data from our previous study of creatine and minocycline,[23] the timing of the initiation of dopaminergic therapy in early PD appears to have changed

since the time of the DATATOP study. Specifically, individuals are started on dopaminergic therapy earlier in their disease course (figure 3) when they have a smaller deterioration in UPDRS scores (table 3). The combined effect of this change is to reduce the decline in UPDRS scores in untreated patients. Table 4 lists the observed annual change in the UPDRS and its subscores, the Hoehn & Yahr Stage and the Schwab & England ADL scores.

Given the evidence that the DATATOP placebo cohort is not reflective of current clinical practice, an exploratory sensitivity analysis was performed based on the calibration placebo groups from this and the prior futility study as well as an additional placebo group (n = 200) from a separate concurrent trial in early PD.[41] Using only data from these placebo groups (not including DATATOP), the threshold value was re-computed as 4.96, and both CoQ_{10} and GPI-1485 would be futile using this threshold value (table 2). The same exploratory analysis was applied to the data obtained from the prior futility study evaluating creatine and minocycline (referred to as FS1).[23] This analysis indicated that minocycline is futile, whereas creatine futility was not detected in any analysis (table 2).

Safety and tolerability. CoQ_{10}, GPI-1485, and the matching placebo formulations were generally well tolerated. Study drug was prematurely discontinued in 4 subjects (6%) in the CoQ_{10} arm (possible allergic reaction, heartburn [2], withdrew consent), 8 subjects (11%) in the GPI-1485 arm (pregnancy, heartburn [3], depression, fatigue, weight loss, difficulty swallowing), and 7 subjects (10%) in the calibration placebo arm (IRB concerns about vitamin E [2], blood clot, low platelets, nausea, prostatitis, change in urine color). Subjects who prematurely discontinued treatment were encouraged to continue to participate in the protocol-specified data collection. Some subjects also discontinued participation in the study before completion: three in the CoQ_{10} arm (moved, lost to follow-up, "lack of benefit"), two in the GPI-1485 arm (moved, IRB concerns about vitamin E), and three in the placebo calibration group (moved [preceded by discontinuation for nausea], physician advised, suicide attempt). One subject in the GPI-1485 arm became pregnant despite oral contraceptive use and discontinued study medication. The pregnancy was carried to term, and no abnormalities were detected in the newborn. There were no differences in the laboratory testing among the treatment groups.

The most commonly occurring adverse events across the three treatment groups were nausea (18%), upper respiratory tract infection (13%), and joint pain (13%) (table 5). One subject in the CoQ_{10} arm had recurrent tongue swelling that represented a possible allergic reaction.

Eighteen SAEs occurred during the study: 4 in the CoQ_{10} group, 8 in the GPI-1485 group, and 6 in the placebo calibration group. In the CoQ_{10} group one individual had (each) exacerbation of diverticulosis, a gall bladder disorder, increased coughing, and a recurrence of a kidney stone. In the GPI-1485 group one subject had (each) exacerbation of spinal stenosis and also bursitis, gastritis, arthritis, fracture, angina, deep vein thrombosis, and depression. In the placebo group one subject had (each) syncope, atrial fibrillation, suicide attempt, serious fall, elective urologic surgery, and a TIA. Of the SAEs in the active treatment groups, only one was thought to be possibly related to study treatment, which was the deep venous thrombosis in the GPI-1485 group.

Discussion. This randomized, double blind, futility study showed that neither CoQ_{10} nor GPI-1485 could be rejected as futile in a 12-month evaluation of clinical progression of PD using the prespecified futility threshold. The observed mean changes in total UPDRS scores for both groups were not significantly greater than the predetermined futility threshold value. Based on these findings using the primary prespecified outcome, both of the agents merit further consideration for phase III trials.

However, the progression of UPDRS scores was very small in the concurrent calibration placebo group (6.31), and this rate was lower than that reported in the DATATOP trial (10.46). The results of this study, along with the prior futility study where the mean (SD) change in the calibration placebo group was 8.39 (9.76),[23] raise the possibility that the PD population, medical practice, or both have changed since the 1980s when the DATATOP data were gathered. To determine whether these differences may be due to chance alone, we measured the likelihood of observing placebo responses similar to ours in the DATATOP cohort by drawing 4,000 samples of size 67 (with replacement) from the DATATOP database. The chance of observing a placebo mean of the size observed in the present study or smaller was 0.03%, and the chance of observing a mean of 8.39 or smaller, as in the initial NET-PD futility study,[23] was 4%. These small probabilities suggest that the observed mean changes in the placebo groups were unlikely to have occurred by chance alone. Changes in practice parameters, use of the UPDRS scale, or in the PD population could account for this change.

Based on the primary and secondary analyses (including updating the historical control with the NET-PD placebo groups), both CoQ_{10} and GPI-1485 could be considered for phase III trials. In contrast, an exploratory analysis adjusting the futility threshold using the combined mean from a contemporaneous placebo group from the PRECEPT trial[41] and the placebo groups from our two futility studies suggest that both CoQ_{10} and GPI-1485 are futile. Applying a similar exploratory analysis to the data obtained in the first futility study[23] would suggest that minocycline is also futile, whereas creatine is reasonable to consider for future study. Thus the conclusions of the study would differ based on the data used to construct the futility threshold. Rigorous methodology would suggest we should use our prespecified values. On the other hand, these are exploratory pilot studies aimed at identifying futile agents, rather than establishing efficacy, so more methodologic flexibility is tolerable. Our analyses comparing current results in research studies to those from two decades ago suggest that important changes have occurred. Pilot futility studies have generally been done in clinical conditions where the natural history of the disorder is well characterized and not thought to change over

time. Also, biologic measures rather than clinical scales are frequently used. Because of the differences in PD, we included a calibration placebo group to assess whether the natural history of the disorder had changed. The findings from our calibration placebo groups, as well as a concurrent placebo group in similarly designed independent study, suggest a change has occurred in the UPDRS rating scale over time. Although we anticipated such a change may have occurred, we did not foresee such a large reduction in the UPDRS rate of change. This apparent change in the natural history of early PD progression suggests that using futility pilot studies in PD may not be straightforward. A classic futility design with inclusion of a calibration placebo group as we have done seems preferable. A phase II study designed to make direct comparisons to a concurrent placebo group without use of the historical futility threshold[42] would still require an assumption about placebo response for sample size calculations and would be likely to require a larger sample size, given the possibly high variability in placebo responses. Placebo variability is indicated by the differences in the placebo groups in our two very similar, virtually concurrent groups conducted by the same group of investigators. Further use of these pilot designs will help identify their practicality, feasibility, and ability to identify agents worthy of further study.

An additional consideration in the present study is the presence of 1,200 IU of vitamin E in the CoQ_{10} placebo wafers. It is possible that the low progression rate observed in the placebo group might be explained by a disease-modifying effect of vitamin E. However, all treatment groups received the same amount of vitamin E including the GPI-1485 group. One would therefore expect, if vitamin E were disease modifying, a similarly low change in UPDRS would have been observed in the GPI-1485 group as well. Although it is not possible to exclude the possibility that GPI-1485 inhibited a protective effect of vitamin E, there are several lines of evidence that would not support a disease-modifying effect of vitamin E. The DATATOP trial, which evaluated 800 subjects, failed to demonstrate an effect of 2,000 IU of vitamin E on disease progression.[38] While one could hypothesize that a lower dose of vitamin E may be neuroprotective whereas a higher dose is not, data from the QE2 study evaluating CoQ_{10} and vitamin E at a dose of 1,200 IU do not support this hypothesis; the placebo group had a mean total UPDRS change similar to that observed in DATATOP.[12]

During this trial a meta-analysis was published suggesting that vitamin E could have an adverse effect on mortality.[43] Although other analyses question these findings,[44] one subject in the GPI-1485 group was discontinued from the study and two subjects in the placebo group were permanently discontinued from study medication due to IRB concerns about vitamin E. For one subject, outcomes had to be imputed as the subject had not yet been started on symptomatic therapy. Analyses excluding this subject did not change study results.

The present futility study evaluating GPI-1485 and CoQ_{10} was not designed to determine whether either agent is actually effective in slowing the clinical progression of PD. Randomized, placebo-controlled phase III trials that focus on clinically meaningful outcomes would be needed to prove or disprove the clinical efficacy of these agents. Therefore, neither CoQ_{10} nor GPI-1485 should be used clinically for treatment in PD based on the results of this study. Given the data suggesting there has been a change in practice over time in the initiation of dopaminergic therapy, and given the results of the comparison to a contemporary control rate, the results of this trial do not provide consistent evidence for evaluating minocycline, GPI-1485, or CoQ_{10} in a phase III trial. It must also be kept in mind that additional factors must be weighed before selecting agents for phase III trials. These factors include the observed safety and tolerability of the agents as well as the costs and availability of these and other agents currently being tested in phase III trials. In particular, an independent large clinical trial of CoQ_{10} funded by NINDS is planned.

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