Published in final edited form as:
Mov Disord. 2012 October ; 27(12): 1513–1521. doi:10.1002/mds.25175.

Design innovations and baseline findings in a long-term Parkinson's trial: NET-PD LS-1

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Abstract

Background—Based on the pre-clinical and the results of a phase 2 futility study, creatine was selected for an efficacy trial in Parkinson's disease (PD). We present the design rationale and a description of the study cohort at baseline.

Methods—A randomized, multicenter, double-blind, parallel group, placebo controlled Phase 3 study of creatine (10 gm daily) in participants with early, treated PD, the Long-term Study – 1 (LS-1) is being conducted by the NINDS Exploratory Trials in Parkinson's Disease (NET-PD) network. The study utilizes a global statistical test (GST) encompassing multiple clinical rating scales to provide a multidimensional assessment of disease progression.

Results—A total of 1,741 PD participants from 45 sites in the U.S. and Canada were randomized 1:1 to either 10-gm creatine/day or matching placebo. Participants are being evaluated for a minimum of 5 years. The LS-1 baseline cohort includes participants treated with dopaminergic therapy and generally mild PD.

Conclusions—LS-1 represents the largest cohort of patients with early treated PD ever enrolled in a clinical trial. The GST approach should provide high power to test the hypothesis that daily administration of creatine (10gm/day) is more effective than placebo in slowing clinical decline in PD between baseline and the 5 year follow-up visit against the background of dopaminergic therapy and best PD care.

Keywords

neuroprotection; Parkinson's disease; clinical trial; creatine; global statistical test

Introduction

Clinical trials in Parkinson's disease (PD) face several challenges that have limited their ability to detect meaningful clinical slowing of disease progression. Two specific obstacles, the lack of an agreed upon, appropriate outcome measure of disease progression and the confounding effect of robust symptomatic benefits of current PD treatments hamper current trial design and the interpretation of the results. The NINDS Exploratory Trials in Parkinson's Disease (NET-PD) network developed the Long-term Study – 1 (LS-1) in response to these challenges. The LS-1 trial is a multicenter, double-blind, parallel group, placebo controlled, randomized Phase 3 study of creatine in participants with PD receiving dopaminergic therapy per standard of care, and is conducted by the NINDS Exploratory Trials in Parkinson's Disease (NET-PD) network (ClinicalTrials.gov Identifier NCT00449865).

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Scientific Rationale

Using an innovative, evidence-based process for the identification and evaluation of potential therapies for the slowing of PD progression, a multi-disciplinary panel conducted a systematic review to identify key potential compounds. This was based on the strength of evidence from the preclinical and clinical data (scientific rationale, efficacy in animal models, safety and tolerability, blood–brain barrier penetration)[1]. The NET-PD program conducted two clinical trials of four selected potential therapies (creatine, minocycline, coenzyme Q10 (CoQ10), and GPI-1485)[2;3]. These selected potential therapies were evaluated using a futility study design. Therapies not found to be futile would be recommended for further study in a large, simple trial for efficacy. The results of both futility trials and the extension study consistently supported the further study of creatine, while evidence was inconsistent for minocycline, GPI-1485, or CoQ10[2–4].

Although the etiology of PD is incompletely understood, evidence suggests roles for oxidative stress and mitochondrial dysfunction[5–7]. Pre-clinical studies indicated that creatine exerts antioxidative properties, affects mitochondrial energy production, and protects against MPTP-induced dopamine depletion[7–9]. In this context, creatine mechanisms of action might be effective at directly or indirectly slowing this process of clinical decline. Creatine could support or augment mitochondrial function by acting as an energy buffer, by acting indirectly as an antioxidant, and by antagonizing mitochondrial permeability[8]. Creatine is a natural derivative of the amino acids arginine and glycine. Cells primarily use creatine in the intermediate form of phosphocreatine which serves as a phosphate donor to generate ATP from ADP. Creatine supplementation has most commonly been used by athletes to improve performance. Oral supplementation of creatine leads to increased plasma free creatine, increased muscle and brain creatine and phosphocreatine, and may lead to enhanced athletic performance[10–13].

Study Objective

The primary objective of the study is to test the hypothesis that daily administration of creatine (10gm/day) is more effective than placebo in slowing clinical decline in PD between baseline and the 5 year follow-up visit against the background of dopaminergic therapy and best PD care. Given that PD is a multi-factorial disease that contributes to motor, cognitive, and behavioral disability, a global outcome measure of clinical decline is utilized to provide sensitivity in detecting overall changes in disease state. The study global outcome is comprised of 5 measures: Schwab and England ADL, Parkinson's Disease Quality of Life (PDQ-39), Unified Parkinson's Disease Rating Scale questions related to ambulatory capacity, Symbol Digit Modalities, and Modified Rankin, and is analyzed by a Global Statistical Test (GST). The primary hypothesis is that clinical decline after 5 years of follow-up as measured by the mean summed rank of the five primary measures (modified Rankin score, Schwab and England, ambulatory capacity, PDQ-39 summary score, symbol digit modalities) in the creatine arm will be less than the mean summed rank of the five primary measures in the placebo arm.

Design Rationale

The trial was not designed to distinguish a disease modifying effect from a symptomatic effect, but rather, to determine if long-term treatment group differences could be found, even as participants received individually optimized PD symptomatic therapy. Recent PD trials enrolling early, untreated patients have shown that nearly half of the participants will require symptomatic therapy within one year[3]. By requiring participants to be receiving dopaminergic therapy before randomization, we hoped to target participants who were at or near their maximum benefit from such therapy at the time of enrollment. Thus we would

avoid the dramatic but variable improvement that commonly occurs when patients first begin dopaminergic therapy[14].

Model-based estimates suggest that maximum motor benefit is achieved approximately 6 months after initiation of dopaminergic therapy, and motor decline is steady after that point even in the presence of dopaminergic dosage adjustments[15]. We sought participants who were early enough in the course of the disease that, if treated, they might reasonably be expected to benefit from therapy. At the same time, we sought to evaluate patients over a sufficiently long period of time such that progression of those features causing clinical disability (motor signs, balance impairment, cognitive decline) could be observed, despite optimal treatment with currently available therapies. Hence, we sought to determine if the addition of creatine could provide long-term clinical benefit beyond that which can be achieved by optimal dopaminergic therapies, which is of relevance to its potential use in clinical practice. This definition of the target study population required fewer participants than enrolling participants at a more advanced stage of PD who would be less likely to benefit from a disease modifying therapy. Similarly, allowing enrollment to include a mixture of treated and untreated participants would have made the cohort less homogeneous and would require a larger sample size[15].

Given that PD is a multi-faceted disease, there is no single clinical measurement that reflects the full range of PD signs and symptoms. The gold standard rating scale, the Unified Parkinson Disease Rating Scale (UPDRS)[16], is focused on classic PD motor features and is less sensitive to “non-motor” symptoms. A multiple endpoint approach using a GST is a useful and efficient method of combining information from a set of validated measures, and this approach may provide a broader assessment of clinical decline[17;18]. The GST has been widely used in clinical trials (including neurological applications such as the NINDS rTPA stroke trial), and its usefulness in studying PD has been described in detail previously[17;18].

Participant Eligibility Criteria

The target population was patients with early stage PD (within 5 years from diagnosis) who were receiving dopaminergic therapy for symptom control. To be eligible, participants must have taken dopaminergic therapy (levodopa or a dopamine agonist) for at least 90 days but no more than 2 years (Supplementary Table 1). Following baseline evaluation and the initiation of study medication, participants could receive any available PD therapies, with changes permitted over time to allow individual optimization of therapy.

Data Collection

Participants will be followed until the last enrolled participant has completed five years of observation. Thus, many participants will have extended follow-up, to a maximum of 8 years (with the average length of follow-up expected to be 6.5 years). In-person evaluations are conducted at baseline, 3 months, 6 months, 12 months, 18 months, and then annually beginning at 24 months with telephone calls every 6 months.

Outcome Measures

Five outcome measures representing simple, brief assessments in clinically relevant domains (activities of daily living, cognitive function, ambulatory capacity, quality of life, and global disability) were chosen based on a consensus of the NET-PD Steering Committee (comprised of five physicians specializing in movement disorders, one study Coordinator, and one Biostatistician) after consultation with the participating NET-PD site investigators and the sponsor’s oversight boards. These outcome measures are combined using a GST into a single primary outcome.

The following measures are included in the 5-year primary outcome: *change from baseline* in modified Schwab and England[16,19] (activities of daily living), Symbol Digit Modalities-verbal[20] (cognitive function), PDQ-39[21] (quality of life), and ambulatory capacity (sum of 5 UPDRS questions: Q13 falling, Q14 freezing, Q15 walking, Q29 gait, Q30 postural stability) and *the 5-year measurement* of modified Rankin Scale (global disability)[22]. Additional outcome measures are collected for secondary analyses including: UPDRS Parts I-IV[16], Beck Depression Inventory II (BDI)[23], Total Functional Capacity[24], SCOPA-COG[25], and EuroQOL (EQ-5D)[26].

Statistical Analysis

The primary analysis will compare the observed mean summed ranks of the five efficacy measures listed above in the creatine arm to the placebo arm in a nonparametric GST, adjusted for site[27;28]. All measures are coded such that higher values are worse (reverse coding some measures). Next, the summed ranks for a participant will be computed by ranking each participant on each measure (across both treatment arms) and then summing the ranks for each participant. If the GST is statistically significant, univariate testing of the individual outcomes measures will be conducted at the two-sided nominal level of 0.05. This approach provides weak protection of the type I error rate. When the treatment effect is consistent across all the measurement domains, then the GST approach is more powerful than any single metric. However, if the treatment is beneficial for one outcome but demonstrates no effect on (or worsens) other outcomes, the GST will lose power to detect a treatment difference, and the GST would likely fail to show a difference between groups.

In LS-1, participants have the option of stopping study drug, but continuing to be followed at regular study visits thereby minimizing the amount of missing data. The primary analysis for LS-1 will be will be analyzed under the intent-to-treat (ITT) principle and will include all participants who were randomized regardless of discontinuation of study medication, noncompliance or protocol deviations. The primary analysis will incorporate missing data using a multiple imputation method based on item response theory that takes into account correlations among outcomes and is preferable to standard methods, such as last observation carried forward[29]. As a sensitivity analysis we will also do an analysis of those for whom we have efficacy data at 5 years; those participants who die will be given the worst possible score.

When 25% and 50% of participants have completed 5 years of follow-up there will be formal interim analyses of the primary outcome to consider stopping the trial early for efficacy or for lack of power to show an effect. Prior to the first interim analysis we assessed the variability of the outcomes used for the sample size estimates for the placebo group, and we could not detect a difference from our hypothesized values so the trial continued without a sample size increase.

Sample Size

Using the prior NET-PD studies, available literature, and clinical trial data on patients similar to the LS-1 target population, mean and variance estimates of annual rates of change were obtained. With permission from the trial Executive Committees, patient-level data from prior PD clinical trials were used: CALM-PD (Comparison of the Agonist Pramipexole versus Levodopa on Motor Complications of Parkinson's Disease) and DATATOP follow-on protocols PEP/PEPX (Primary Endpoint Protocol)[30;31]. The first measurement 3 – 6 months after initiation of dopaminergic therapy was considered the baseline measurement to imitate the LS-1 inclusion criteria. For the modified Rankin scale of global disability and the Symbol Digit Modalities, no data were available for treated PD patients and estimates from untreated PD patients and from normal elders were used[2;3;32–34]. Although a GST is the

primary analysis, we powered the study such that there would be sufficient sample size to detect an effect, if one existed, for each univariate measure.

The minimum clinically meaningful difference was chosen to be a 1 year improvement in each measure, meaning that at 5 years the treatment arm progression is equivalent to progression in the placebo group at 4 years. Thus, progression (based on each measure) has been slowed by 1 year. With 549 per group there is at least 85% power to detect a 1 year improvement in the treatment arm compared to control for change from baseline in Schwab and England ADL, change from baseline in PDQ-39, and 5 year Modified Rankin values. Likewise, this sample size provides 85% power to detect a ~1.5 year improvement in the treatment arm compared to control for the change from baseline in ambulatory capacity and change from baseline in Symbol-Digit Modalities (in a two-sample *t*-test assuming two-sided alpha of 0.05 and interim analyses). The 1 year difference in means (SD) are 2 (11), 3 (9), 0.2 (1), for Schwab and England ADL change[2;3;31], PDQ-39 change[35], and 5 year Modified Rankin values[2;3;32], respectively[2;3;31;35]. The 1.5 year difference in means (SD) are 0.383 (2.1), 1.5 (8), for ambulatory capacity change[30;31] and Symbol-Digit Modalities change[33;34], respectively. Using the GST, this sample size (549 per group) will provide 99% power at the alternative global treatment effect (GTE) value of 0.1189 assuming the maximum correlation among outcomes is 0.50[36,18]. The GTE is estimated from the means and SD given above for each measure and has been previously described[28]. The power of the GST assumes a common treatment effect across all outcomes and will be less powerful if this assumption is not true. The total sample size was inflated from 1098 to 1720 (860/treatment group) to account for an expected drop-out or nonadherence rate of 20% over 5 years in the intent-to-treat (ITT) sample[37] (where the inflation factor is equal to $1/(1-0.20)^2$).

Enrollment Process

Between March 13, 2007 and May 28, 2010, a total of 1,741 PD participants from 45 sites in the U.S. and Canada were randomized 1:1 to either 10-gm creatine/day or matching placebo. Each participant gave written informed consent. The protocol and consent forms were approved by the institutional review boards (IRBs) of each of the participating sites. Recruitment was completed in just over three years, slower than the targeted recruitment period of two years, in part, due to delays in drug supply. In September 2008, the independent Data Safety Monitoring Board (DSMB) reviewed the LS-1 safety data and recommended modifications to the protocol to address elevated creatinine levels in some participants. Participants already enrolled were allowed to remain in the study, but discontinued study drug if they met alert criteria for creatinine or eGFR. Participants with reduced renal function (eGFR< 50 mL/min/1.73m^2 at baseline) who were randomized after September 16, 2008 were discontinued from study drug immediately. These participants were asked to return for a single premature withdrawal visit (n=15). The primary analysis will include all 1741 participants enrolled, but follow-up data will be imputed for these 15 individuals.

Baseline Characteristics

On November 14, 2011 the LS-1 baseline database was frozen. The baseline demographics and clinical characteristics of this cohort are presented in Tables 1 – 5. The LS-1 baseline cohort includes participants with on average, mild motor impairment, minimal cognitive impairment, at most mild depressive symptomatology, no significant disability, and mild impact on quality of life. Compared to studies of prevalence and incidence of PD by age, gender, and ethnicity, the LS-1 cohort is similar in gender distribution to other reports[38;39], but enrolled younger patients than expected (the average age was 61.8 years old (SD=9.6)

and most LS-1 patients were concentrated in the age range of 50–69).[40] (See supplementary figure 1). Despite extensive efforts to enroll diverse participants, the LS-1 trial enrolled more non-Hispanic whites than expected based on population incidence rates by race/ethnicity, but this was similar or better than other clinical trial enrollment rates of minority participants[39;41]. Participants tended to be well-educated and most were living at home without outside care, and over half were working full-time (39%) or part-time (13%). Sixty-three percent had a primary occupation that could be considered management or professional for most of their career. See Table 1.

Discussion

Several clinical trial designs have been used to differentiate symptomatic from disease modifying effects. However, none has been entirely successful, as wash-in and wash-out of symptomatic effects may evolve over prolonged and uncertain periods of time and will vary based on the intervention[42]. An alternative approach is to determine whether a therapy provides long term additional benefits over and above those that can be achieved with current therapies, regardless of the nature of the treatment effect. Past trials of disease modifying drugs have been conducted in participants who were early in their disease course and not receiving symptomatic therapy. A considerable number of participants require dopaminergic therapy in the course of such studies thus limiting the value of the data collected from the long term follow up.

The LS-1 design rationale was to target participants still early enough to benefit from a disease modifying drug and to follow them for long enough to demonstrate such benefit. To minimize potential confounding due to the initiation of concomitant, symptomatic PD drugs, the LS-1 design enrolled participants with early PD, who were already treated with dopaminergic therapy for a common exposure period. Considering increased use of dopaminergic therapy as a negative outcome, a secondary analysis will compare the total cumulative levodopa-dose equivalency over 5 years in the creatine group versus the placebo group. Allowing participants to be individually, appropriately treated reflects real-world practice, appeals to participants and families, and may help to retain participants for long term follow-up.

Although there is no other study that is directly comparable to LS-1, the cohort's PD characteristics appear to be close to what might be anticipated with the study inclusion criteria. One recent study compared treatment with carbidopa/levodopa/entacapone (C/L/E) to carbidopa/levodopa (C/L) at a dose of 300 mg/day for 39 weeks in early untreated patients who required levodopa therapy. At the end of the study, mean duration since PD diagnosis was 1.9 years, and total UPDRS (I-III) was approximately 25.9 (C/L/E) or 27.4 (C/L)[43]. This is similar to the LS-1 population in which mean duration since PD diagnosis was 1.5 years, mean total daily LD dose equivalent at baseline is was 354 mg, and mean total UPDRS (I-III) was 26.2. However, subjects in the C/L/E vs. C/L study were older (64.8 years) than those in the LS-1 study (mean age 61.8 years), possibly because the former study excluded subjects on dopamine agonists. Compared to recent trials enrolling early untreated patients, the LS-1 patients are comparable in age, but have had the disease for slightly longer than patients in the TEMPO, ADAGIO, and ELLDOPA trials (1.5 versus less than 1 year) [44–46]. The clinical rating scales of LS-1 patients are similar to the untreated UPDRS and Schwab and England ADL scores in TEMPO and ELLDOPA patients, suggesting that the LS-1 patients are indeed appropriately treated with dopaminergic therapy and represent the desired population.

Lessons to be learned

Historically, long-term clinical trials of PD patients have considerable attrition, in many cases more than 30%[30;48–51]. In planning LS-1, a 20% rate of drop-outs or study drug non-adherence was assumed. Although LS-1 participants are encouraged to continue follow-up even after discontinuation of study drug, participants who discontinue medication or who are only partially compliant still represent an obstacle to identifying an effect of study treatment if such an effect occurs. The sample size inflation factor used assumed that the average proportion of assigned treatment that is actually received over 5 years will be 80%. Although the drop-outs or study drug non-adherence rate may be optimistic, the GST was highly overpowered at greater than 99%; thus even if the drop-outs or study drug non-adherence rate is 30%, the GST has power of at least 95% to detect the specified effect. Currently, innovative approaches to reducing the dropouts or study drug non-adherence rate are being used including teleconferences with trial participants to discuss the importance of continued participation and to address any questions. Efforts are being made to increase the flexibility of clinic hours and to address other barriers to participation.

A substudy attempted to increase minority recruitment but was not successful[47]. Focused efforts with substantial resources will be needed to understand and overcome the barriers to minority participation in PD research.

Conclusions

In conclusion, LS1 represents the largest cohort of patients with early treated PD ever enrolled in a clinical trial. Although the cohort includes more younger patients and more non-Hispanic whites than expected based on epidemiological studies, the size of the cohort, broad inclusion and limited exclusion criteria, flexible dosing of symptomatic medications optimized by the treating physician, the large number of clinical sites involved in the US and Canada, and the similarities with other clinical trials suggest the findings of this baseline cohort may be generalizable to an early PD clinical population already receiving symptomatic treatment in the US and Canada. While some of the clinical rating scales collected at baseline were validated in smaller samples, this study provides an opportunity to assess these scales in a larger cohort of early PD patients. In addition to the primary objective, the long term follow-up of this homogeneous target population (dopaminergic treated patients beginning the trial early in their course of PD) will provide a rich database to learn more about many features of PD.

The study utilizes a GST, the individual components of which provide multidimensional assessment of disease related disability, and participants, receiving dopaminergic therapy and best PD care, are followed for an extended period of time. Even in the face of a higher than expected percentage of drop-outs or study drug non-adherence, the novel GST approach should provide high power to detect an effect of creatine on clinical decline in PD, if one exists. While the size and duration of the trial is daunting, the recruitment and retention of research subjects and investigative sites appears feasible. The longitudinal data will be useful in determining if future studies in this population can possibly be smaller and shorter, yet still be able to detect meaningful differences in clinical decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

LS1 Participants

We thank the patients and families who participate in the LS-1 study.

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Funding/Support: This study was sponsored by the National Institutes of Health (NIH), National Institute of Neurological Disorders and Stroke. The authors report no other financial disclosures related to the content of this manuscript.

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Full financial disclosure for the previous 12 months

1. Dr. Elm has research grant support from NIH and was a consultant for Teva.

2. Dr. Augustine is funded by NIH grant #NS066098, and receives research support from the Food and Drug Administration #003908-01, Tourette Syndrome Association and Batten Disease Support and Research Association.

3. Dr. Aminoff has received royalties from publishing Neurology & General Medicine (Elsevier, 1989–2011), Electrodiagnosis in Clinical Neurology (Elsevier, 1980–2011), Clinical Neurology (McGraw-Hill, 1989–2011), chapters in Cecil Textbook of Medicine (W.B. Saunders; 2004 and 2008), Harrison's Principles of Internal Medicine (McGraw-Hill, 1994–2011)), Handbook of Clinical Neurology (Elsevier; 2003–2011), and Current Medical Diagnosis & Treatment (McGraw-Hill, 1985–2011); has received honoraria for lectures or educational activities not funded by industry; serves as Editor-in-chief, Neurology section, Up-to-date, for which he receives royalties; served as a paid consultant to iPerian Inc. and Biovail Ltd.; and receives research support from Genzyme Corporation, the Michael J. Fox Foundation, the NIH [NINDS #5 U10 NS044460 (Site PI) and #R01 NS37167 (Site PI)] and the University of Rochester.

4. Ms. Bennett reports no financial disclosures.

5. Dr. Bodis-Wollner has research grant support from the Michael J Fox Foundation.

6. Dr. Cambi reports no financial disclosures.

7. Ms. Carter receives research support from NIH, NPF and MJFF. She has received honoraria from Teva.

8. Dr. Chou receives research support from the NIH (NS44504-08), participates as a site-PI in clinical trials sponsored by the HSG (PHAROS, 2CARE, and CREST-HD), receives royalties from UpToDate, and has received honoraria from Medtronic and Merz Pharmaceuticals for consulting work.

9. Dr. Christine has received research support from Genzyme Corporation, Kinemed, and the NIH, through grants to UCSF.

10. Dr. Dewey has served as a consultant to Teva, Noven, and Merz pharmaceuticals, has participated in speaking programs sponsored by Teva, GlaxoSmithKline, Ipsen, and Allergan, and has performed research funded by NIH.

11. Dr. Dhall reports no financial disclosures.

12. Dr. Elble is a paid consultant for the Kinetics Foundation. He received grant support from GlaxoSmithKline, Phytopharm and TEVA. He received other funding support from NINDS and the Spastic Paralysis Research Foundation of Kiwanis International, Illinois-Eastern Iowa District.

13. Dr. Fang reports no financial disclosures.

14. Dr. Feigin served as a speaker for Allergan, Teva, and Boehringer-Ingelheim.

15. Dr. Galpern reports no financial disclosures.

16. Ms. Gardiner reports no financial disclosures.

17. Dr. Goudreau has research support from: NINDS, MJ Fox Foundation, TEVA, Allergan. He is on the Speaker's bureau for TEVA.

18. Dr. Harman reports no financial disclosures.

19. Dr. Hauser has received honoraria or payments for consulting, advisory services, speaking services or research over the past 12 months as follows. Advisory Board: Boehringer Ingelheim Pharmaceuticals, Inc., Teva Neuroscience, Impax

Pharmaceuticals, UCB, Inc., GE Healthcare, IPSEN Pharmaceuticals, Novartis, Parkinson Study Group, Solvay, Quintiles, Biogen Idec. Speakers Bureau: Allergan Neuroscience, GlaxoSmithKline, TEVA Neuroscience, Boehringer Ingelheim Pharmaceuticals, Inc., Novartis Pharmaceuticals, IPSEN Pharmaceuticals. Consulting: Bial, Lundbeck, Biogen Idec, Boehringer Ingelheim, Chelsea Therapeutics, GE Healthcare, Impax, Santhera Pharmaceuticals, Merck Serono/ EMD Serono, Solvay Pharmaceuticals, Synosia Therapeutics, Schering-Plough, Shire Pharmaceuticals, Inc., XenoPort, Inc., Medivation, Inc., Addex, Adamas Pharmaceuticals, Noven Pharmaceuticals. Research: PICO-Tesla, Schwartz Pharma, Genzyme, Acadia, Solvay Pharmaceuticals, Impax, TEVA Neuroscience, (Merck) Serono, Schering-Plough, Novartis Pharmaceuticals, IPSEN Pharmaceuticals, XenoPort Pharmaceuticals, Chelsea Therapeutics, Allergan Neuroscience, Molecular Biometrics, The Michael J. Fox Foundation for Parkinson's Research, and the National Parkinson Foundation. Royalties: University of South Florida. In addition, Dr. Hauser has consulted in litigation with lawyers representing various current and former manufacturers of welding consumables.

20. Dr. Juncos reports no financial disclosures.

21. Ms. Kamp reports no financial disclosures.

22. Dr. Keiburtz reports the following financial disclosures. He is a consultant for National Institutes of Health (NINDS), the United States Food and Drug Administration, the United State's Veteran's Administration, Abbott, Acorda, Biogen Idec, Biotie, Biovail, Boehringer Ingelheim, Ceregene, Civitas, Clintrex, Cynapsus, EMD Merck Serono, Genzyme, Impax, Intec, Ipsen, Isis, Knopp, Lilly, Link Medicine, Lundbeck, LZ Therapeutics, Merz, Novartis, Orion, Otsuka, Pharm2B, Phytopharm, Schering-Plough, Siena Biotech, Synosia, Solvay, Synagile, Teva, UCB Pharma, Vaccinex, Xenoport. He received Grants/Research Support from: Medivation, Michael J. Fox Foundation, National Institutes of Health (NEI, NINDS, NIA, NICHD), Neurosearch, Pfizer. He received other support (legal consulting) from Pfizer and Welding Rod Litigation Defendants.

23. Dr. Leehey reports the following funding sources: Neurologix, Inc.; NIH/NINDS, Schwartz Biosciences, Inc.; Michael J Fox Foundation, IMPAX Pharmaceuticals, FDA

24. Dr. Lew reports the following disclosures: He was a speaker- Boehringer-Ingelheim, Teva, Solstice Neurosciences, Ipsen. He was an Advisor/consultant for Teva, BI, Solstice Neurosciences, Novartis, Ipsen, Schering Plough, GSK, Merz, Abbott, Impax. His research activities were supported by NIH, Abbott/Solvay, Schering Plough, Parkinson's Study Group, Michael J. Fox Foundation, Allon Therapeutics, Addex, Takeda Pharmaceuticals, Synosia Pharmaceuticals, Adamas. Foundation Grants- National Parkinson's Disease Foundation (NPF), HollyRod Foundation.

25. Dr. Liang has received research support from Teva Neuroscience and the Kinetics Foundation, has served as a consultant for Chelsea Therapeutics, and has served on the speaker's bureau for Teva.

26. Dr. Lyons has served as a consultant for Adamas, St. Jude Medical and Teva Neuroscience.

27. Dr. Mari is employed at Johns Hopkins University. His research is supported by grants (as managed and appropriated by Johns Hopkins University) from the National Institutes of Health, the Michael J. Fox Foundation, Allergan, Merz, the

National Parkinson Foundation, and Abbott. He receives support for continuing medical education programs supported by Ipsen, Allergan, and Merz, approved and credited by Johns Hopkins University and managed by Johns Hopkins Advanced Studies in Medicine. Dr. Mari has received honoraria for consulting from L.E.K. Consulting LLC, Merz, Ipsen, Allergan, Easton Associates and served as paid consultant and/or medical expert witness for Edwards Angell Palmer & Dodge LLP, Comerford & Britt LLP and BURG SIMPSON ELDREDGE HERSH JARDINE PC.

28. Dr. Martin received research support from NIH, CIHR, Michael J Fox Foundation, Phytopharm, Biotie, Chelsea, and Neurosearch. He served on advisory boards for Allergan, Merz, Chelsea and Teva.

29. Dr. Nance reports speaking honoraria from Augsburg College, Huntington Disease Society of America, American Academy of Neurology; royalties from Oxford University Press; Scientific review panel reimbursement from NIH, PSG; Grant support from Huntington Disease Society of America, National Parkinson Foundation, Michael J Fox Foundation/Northwestern Dixon Foundation, Schwarz Biosciences, Impax Pharmaceuticals, IMPAX Pharmaceuticals, Medivation/Pfizer, Neurosearch Santhera PharmaceuticalsTEVA, NIH/NINDS, NIH/NHGRI, NIH/NCCAM; spouse on Speaker's bureau for Roche.

30. Dr. Pahwa received grants from NIH, NPF, Teva Neuroscience, Novartis, Xenoport, Impax, EMD Serono, Allon, Acadia, Schering, Biotie, Phytopharm, Adamas. He received personal compensation from: Novartis, Teva Neuroscience, Medtronic, St Jude Medical, GE Healthcare, EMD Serono, Adamas, Impax, Medscape. He served on a DSM committee for: Ceregene. He received royalties from: Oxford Press, Informa Healthcare. He is CoEditor in Chief: International Journal of Neuroscience.

31. Dr. Parashos is a shareholder and an employee of the Minneapolis Clinic of Neurology Ltd., a for-profit entity. He has received honoraria from Teva. Dr. Parashos' spouse holds stock of St. Jude Medical, valued in excess of $10,000. Dr. Parashos participated in clinical and drug trials sponsored by the National Institutes of Health, the National Parkinson Foundation, the M J Fox Foundation, Schering-Plough, Biotie, Phytopharm, Schwarz, Impax, and Teva.

32. Dr. Petrovich has received salary support from NIH and DoD grants and from the non-profit research institute, the Pacific Health Research & Education Institute.

33. Dr. Racette reports no financial disclosures.

34. Dr. Ravina is an employee of Biogen, Inc.

35. Dr. Ross reports his sole salary source is the Veterans Affairs Pacific Island Health Care System. He receives funding support from the Department of Defense, NINDS, NIA, Northwestern Foundation and Michael J Fox Foundation.

36. Dr. Sage received support from the NIH and from the American Parkinson Disease Association.

37. Dr. Shulman receives research support from the NIH and Michael J. Fox Foundation. Dr. Shulman serves as Editor-in-Chief of the American Academy of Neurology's Neurology Now Patient Book Series, receives royalties from Johns Hopkins University Press, and receives research support from the National Institutes of Health (U01AR057967-01), the Michael J. Fox Foundation, Teva Pharmaceuticals and the Rosalyn Newman Foundation.

38. Dr. Simon is funded by research grants from the NINDS (1R01NS058988; 1R21NS077758, and U10 NS44482), the NIA(1R03AG035223) and the Michael J. Fox Foundation. He also has a research grant from GE Healthcare and has received consulting fees from Genzyme; Civitas Therapeutics; the Gerson Lehrman Group; Rupert Case Mngmnt, Inc; and Bengston & Jestings, LLP.

39. Dr. Simuni received research support form NINDS, MJFF, NPF, Northwestern Dixon Foundation, participates as a site PI in clinical trials sponsored by PSG, IMPAX, Synovia, TEVA, Phytopharm, served on the advisory boards and speaker for TEVA, GE, Novartis, Ibsen and received honoraria for consulting from Merz, Ibsen, GE, IMPAX, Allergan.

40. Dr. Singer received grants from Boehringer-Ingelheim, Schwartz-Pharma, TEVA, Allergan, Merz, Ipsen, Synoisa/Biotie. IMPAX. He received honoraria for advisory board participation from Ipsen and Lundbeck and honoraria for consultation from Merz, IMPAX and Allergan

41. Dr. Slevin serves/has served on speakers' bureaus for Boehringer Ingelheim, Novartis, and Teva Pharmaceutical Industries Ltd.; and receives research support from Solvay Pharmaceuticals, Inc./Abbott., the US Department of Veterans Affairs, and the NIH.

42. Dr. Suchowersky receives research funding from NIH, CIHR and Abbott. She serves on Advisory boards for Actelion, Allergan and Merz.

43. Dr. Tanner was a consultant for Impax Pharmaceuticals and Adamas Pharmaceuticals and received research grant support from the Michael J. Fox Foundation, Brin Foundation, James and Sharron Clark, the Parkinson's Institute and Clinical Center, Parkinson's Disease Foundation, Department of Defense USAMRAA (TATRC managed NETRP Program), National Institute of Neurological Disorders and Stroke (NINDS), and Agency for Healthcare and Research Quality (AHRQ).

44. Dr. Tilley serves/has served on DSMB for Novartis, Pfizer and receives research support from the Movement Disorders Society and NIH grants.

45. Dr. Videnovic reports no financial disclosures.

46. Dr. Voss received grant support from Teva. She was a consultant for NIH (research proposal review). She received support through contracts with University of Rochester.

47. Dr. Walker reports research funding from NIH/NINDS K23-NS067053-01.

48. Dr. Wills received support from the: Muscular Dystrophy Association, Accordant CVS/Caremark (consultant fees), and Schering-Plough (research support).

49. Dr. Zweig reports no financial disclosures.

Table 1

Demographic Characteristics (N=1741)

	Frequency	Percent
Male Gender	1123	64.5%
Non-Hispanic Whites	1571	90.2%
Education		
< High school	83	4.8%
High school/GED	223	12.8%
Some college/Associate	417	24.0%
Bachelors	477	27.4%
Graduate/professional	541	31%
Right Handed	1540	88.5%
Care Level		
Chronic Care/Full time Skilled nursing	19	1.1%
Home	1722	98.9%
Current Employment Activities		
Working Full Time	669	38.5%
Retired	658	37.8%
Working Part-Time	232	13.3%
Not working, on Disability Pay	72	4.1%
Homemaker	61	3.5%
Unemployed and looking for work	24	1.4%
Other	22	1.3%
Student	2	0.1%
Primary Occupation (most of Career)		
Management/professional	1100	63.2%
Service	223	12.8%
Sales/office	207	11.9%
Farming/fishing/forestry	24	1.4%
Construction/extraction/maintenance	89	5.1%
Production/transportation/material moving	54	3.1%
Not in labor force	44	2.5%

Table 2

Duration of PD and Dopaminergic Therapy Use

	N Observations	Mean	SD
Yrs since PD Symptom Onset	1741	3.3	2.2
Yrs since PD Diagnosis	1741	1.5	1.1
Length of Time on Dopaminergic Therapy (yrs)	1741	0.82	0.7
Levodopa-equivalency total daily dose (mg)[52]	1740	380.3	232.9
PD therapy use, N=1740		**Frequency**	**Percent**
	Levodopa alone	506	29.1%
	Dopamine Agonist alone	463	26.6%
	More than one PD medication *	772	44.3%

* Includes use of levodopa, dopamine agonist, or other PD medications for which there is an established levodopa-equivalency[52].

Table 3

Clinical Rating Scales: Motor, ADL, Function

	N Observations	Mean	SD
Ambulatory Capacity	1739	1.7	1.5
Schwab and England ADL	1740	91.1	6.8
UPDRS Total	1732	26.2	11.4
UPDRS Motor	1733	17.8	8.4
UPDRS ADL	1740	7.2	4.0
UPDRS Motor+ADL	1732	24.9	11.0
Total Functional Capacity (TFC)	1739	12.0	1.4
Modified Rankin Scale[†]		**Frequency**	**Percent**
0 (No symptoms at all)		23	1%
1 (No significant disability despite symptoms)		1344	77%
2 (Slight disability)		345	20%
3 (Moderate disability)		29	2%
4+ (Moderately severe disability/Severe disability)		0	0%

[†]During training, investigators were instructed to only consider symptoms related to PD in scoring the modified Rankin scale. All baseline data was scored in this way. In January 2012 prior to the collection of any 5-year outcome data, the administration of the modified Rankin instrument was changed to indicate that the instrument should be scored as designed, as a global score of disability.

Table 4

Quality of Life

	N Observations	Mean	SD
PDQ-39 Summary Index 0 (no problem) - 100 (maximum)	1738	13.2	10.6
Discomfort	1740	20.8	19.1
ADL	1741	15.0	15.6
Cognition	1741	15.0	15.1
Emotional	1741	14.1	14.9
Stigma	1741	12.9	16.4
Mobility	1739	11.5	16.2
Communication	1741	11.3	14.6
Social	1741	5.3	11.6
EuroQol (Generic Instrument)			
Eq5d Utility Score (1= “perfect health”)	1741	0.8	0.2
Visual Analog Scale (VAS) (100= “Best Imaginable State”)	1739	81.3	13.8

Table 5

Cognition and Mood

	Best possible score	N Observations	Mean	SD
Symbol Digit Modalities * (Total Correct Responses)	110	1736	44.4	11.7
UPDRS Mental	0	1741	1.3	1.4
SCOPA-COG Total *	43	1731	30.3	5.4
		N Observations	**Mean**	**SD**
Beck Depression Inventory (BDI)		1736	6.9	5.5
			Frequency	**Percent**
BDI > 17			83	4.8%

* Higher scores are “better”.