

RESEARCH ARTICLE

A novel design of a Phase III trial of isradipine in early Parkinson disease (STEADY-PD III)

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Abstract

Objective: To describe the rationale for a novel study design and baseline characteristics of a disease-modifying trial of isradipine 10 mg daily in early Parkinson disease (PD). **Methods:** STEADY-PDIII is a 36-month, Phase 3, parallel group, placebo-controlled study of the efficacy of isradipine 10 mg daily in 336 participants with early PD as measured by the change in the Unified Parkinson Disease Rating Scale (UPDRS) Part I-III score in the practically defined ON state. **Secondary outcome** measures include clinically meaningful measures of disability progression in early PD: (1) Time to initiation and utilization of dopaminergic therapy; (2) Time to onset of motor complications; (3) Change in nonmotor disability. Exploratory measures include global measures of functional disability, quality of life, change in the ambulatory capacity, cognitive function, and pharmacokinetic analysis. Rationale for the current design and alternative design approaches are discussed. **Results:** The entire cohort of 336 participants was enrolled at 55 Parkinson Study Group sites in North America. The percentage of male participants were 68.5% with a mean age of 61.9 years (sd 9.0), mean Hoehn and Yahr stage of 1.7 (sd 0.5), mean UPDRS total of 23.1 (sd 8.6), and MoCA of 28.1 (sd 1.4). **Interpretation:** STEADY-PD III has a novel and innovative design allowing for the determination of longer duration benefits on clinically relevant outcomes in a relatively small cohort on top of the benefit derived from symptomatic therapy. Baseline characteristics are similar to those in previously enrolled de novo PD trials. This study represents a unique opportunity to evaluate the potential impact of a novel therapy to slow progression of PD disability and provide clinically meaningful benefits.

Introduction

Parkinson disease (PD) is a significant and increasing public health issue. PD is the second most common chronic neurodegenerative disease, after Alzheimer's disease, affecting nearly 1% of the population over the age of 65.¹ The prevalence of PD is expected to double in the

next 20 years in the world's most populous nations.² The economic burden of PD is estimated to be \$23 billion annually in US and projected to increase to \$50 billion by year 2040.³ Current therapy is limited to symptomatic treatment; however, the disease continues to progress with accumulation of significant disability, worsening quality of life, reduced productivity, nursing home placement,

and increased mortality.⁴ Attempts to slow or modify disease progression in PD have resulted in mixed outcomes and no treatment has yet to definitively demonstrate disease modification (see Table 1 for recent disease-modifying trials).^{5–8} Therefore, treatments that slow disease progression remain a major unmet therapeutic need in PD.

Isradipine, a dihydropyridine calcium channel antagonist (DHP) that is approved for the treatment of hypertension, is being tested as a potential disease-modifying intervention in early PD. Isradipine was shown to be neuroprotective in *in vitro* and *in vivo* models of parkinsonism.^{9,10} The mechanism of neuroprotection is linked to selective vulnerability of substantia nigra pars compacta neurons that preferentially express L-type calcium channels. Neuroprotective effects of isradipine are achieved at the plasma concentration that is obtained within the safe dose range for human administration^{10,11} and consistent with the tolerable dosage identified in our phase II study of isradipine in PD (STEADY-PDII).¹² Isradipine is the most potent of the clinically available Cav1.3 DHPs and has excellent central nervous system penetration suggesting it is the optimal DHP to target this novel mechanism of neuroprotection.^{13,14}

Importantly, multiple epidemiological studies have demonstrated a reduced risk of development of PD in individuals treated with DHPs compared with other antihypertensive agents^{15–17} In addition, 4733 hypertensive individuals with parkinsonism treated with DHPs had a decreased risk of requiring symptomatic therapy (ST), admission to a nursing home, and death compared with those treated with other antihypertensive agents.¹⁸ Although select epidemiological studies have failed to demonstrate this effect, these studies have been limited by small sample sizes and nonrepresentative cohorts.^{19,20} Therefore, convergent data from *in vivo*, *in vitro*, and epidemiological studies strongly support the potential ability of isradipine to slow progression of disability in PD; representing the strongest preclinical and clinical rationale of any past or current putative disease-modifying agent for PD.

In addition to sufficient preclinical and early clinical data, it is critical to use a trial design and outcomes that will be sensitive to clinically meaningful impacts of an intervention above and beyond current ST. Most previous trials (Table 1) have used designs that rely on assessments prior to the initiation of ST or have used the time to initiation of ST as the primary outcome. These studies may

Table 1. Representative Phase III disease-modifying trials in Parkinson disease.

Trial	Intervention	N	Design	PD population	Duration	Primary outcome(s)	Results
DATATOP	Deprenyl and centertocopherol	800	2 × 2 factorial	Early untreated	24 months	Time to development of disability requiring levodopa therapy	Deprenyl resulted in reduced hazard of requiring levodopa therapy
PRECEPT	CEP-1347 10 mg BID 25 mg BID 50 mg BID	806	Parallel group	Early untreated	24 months	Time to development of disability requiring dopaminergic therapy	Terminated early for futility
QE3	Coenzyme Q10 1200 mg/day 2400 mg/day	600	Parallel group	Early untreated	16 months	UPDRS change	Terminated for prespecified futility
ADAGIO	Rasagiline 1 mg/day 2 mg/day	1176	Delayed start	Early untreated	18 months	1) Superiority of UPDRS change in early start to placebo between weeks 12–36 2) Superiority of UPDRS change in early start to delayed start between baseline and week 72 3) Noninferiority of early to delayed start in rate of UPDRS change between weeks 48–72	1 mg/day but not 2 mg/day met all criteria for efficacy
LS1	Creatine	1741	Parallel group	Early stable treatment	60 months	Global statistical test defined by 5 outcome measures: Modified Rankin Scale, Symbol Digit Modalities Test, PDQ-39 Summary Index, Schwab and England Activities of Daily Living scale, and ambulatory capacity (UPDRS)	Terminated due to futility in an interim analysis of 955 subjects followed up for 5 years

be affected by differential drop out and differential use of symptomatic therapies and relatively short duration of follow-up.

STEADY-PDIII (clinicaltrials.gov NCT02168842) is a 36-month, parallel group, double-blind, placebo-controlled trial that will evaluate the effect of isradipine on the progression of PD disability in untreated individuals with early PD.

Methods

Trial design

STEADY-PD III is an ongoing 36-month, double-blind, randomized, placebo-controlled study of isradipine in 336 participants with early PD at baseline not receiving or requiring ST (Fig. 1). This design will test the hypothesis that individuals treated with isradipine will have slower progression of PD disability as determined by the change in the total Unified Parkinson Disease Rating Scale (UPDRS) score²¹ in the active treatment arm versus placebo between baseline and 36 months. Eligible participants are randomized to isradipine 5 mg twice daily or matching placebo. Participants are titrated to the treatment dosage over a period of 4–12 weeks and then followed prospectively and systematically during a maintenance period over the remaining 36 months followed by a 3-day titration off the study drug and 2 week post-titration safety visit. Temporary study drug suspensions are allowed at the discretion of the investigator and participants who permanently discontinue the study drug are encouraged to remain in the study.

Setting

The study is being conducted at 57 Parkinson Study Group (PSG) sites in North America and is funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the Michael J. Fox Foundation. The PSG is an independent consortium of scientific

investigators committed to the cooperative planning, implementation, analysis, and reporting of controlled clinical trials and other research in PD and has successfully completed over 35 multi-center cooperative therapeutic studies including STEADY-PDII.

Participants

Eligible participants have early idiopathic PD (presence of two out of three cardinal manifestations of PD)²²; Age greater than or equal to 30 years at the time of diagnosis; Hoehn and Yahr stage²³ less than or equal to 2; Diagnosis of PD less than 3 years, currently NOT receiving ST (levodopa, dopamine agonist or MAO-B inhibitors) and NOT projected to require ST for at least 3 months from the baseline visit. Use of amantadine and/or anticholinergics is allowed at stable dosages prior to enrollment. The key exclusion criteria include a diagnosis of an atypical parkinsonism; prior exposure to ST, history of orthostatic hypotension (based on standard definitions), bradycardia, congestive heart failure or other cardiac and other systemic diseases, abnormalities on the screening laboratories or ECG that might preclude safe participation in the study; presence of cognitive dysfunction defined by a Montreal Cognitive assessment (MOCA)(104) score < 26;²⁴ clinically significant depression as determined by a Beck Depression Inventory II (BDI-II) score > 15.²⁵ Participants may take up to two other antihypertensives with the exception of calcium channel blockers which are exclusionary.

In addition, participants must meet blood pressure criteria during home blood pressure monitoring prior to initiating study drug.²⁶

Outcome measures

Figure 2 outlines the primary and major secondary outcomes in this study.

The *primary outcome* is the change in total UPDRS (sum of mental, ADL and motor components) from baseline to 36 months in the medications “ON” state approximately 1 h after dose of ST for those receiving symptomatic treatment. The UPDRS is a valid and reliable measure of PD disability that has been effectively used in a number of PD trials.^{21,27,28}

Key *secondary outcomes* of clinical importance have been identified and include: (1) *Time to initiation of ST* has been used as a primary outcome measure in several previous studies of putative disease-modifying agents^{5,29} and reflects progression early in disease not obscured by symptomatic therapy; (2) *Time to and severity of motor complications* may reflect a secondary measure of progression once type of initial symptomatic treatment is

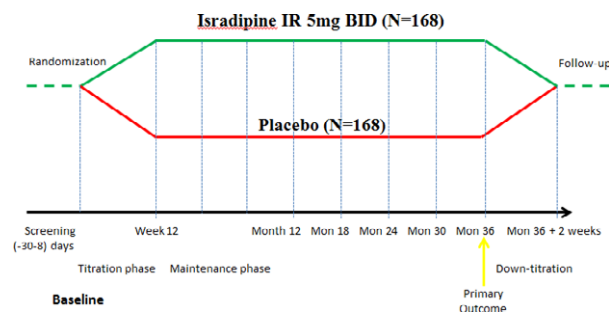


Figure 1. Phase III Study Design.

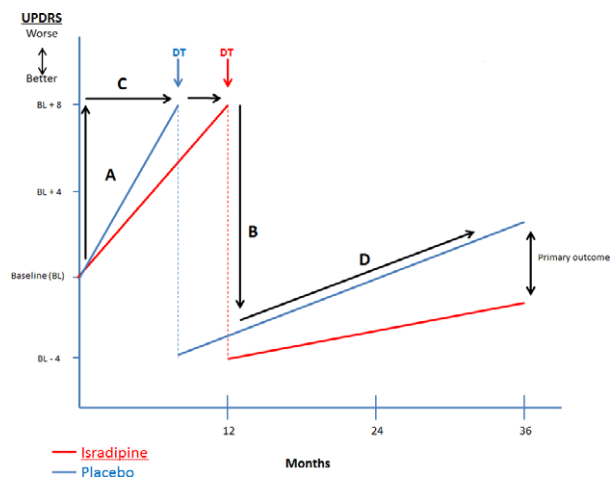


Figure 2. Overview of Efficacy Analyses. Primary outcomes – change in UPDRS from baseline to 36 months. A-change in UPDRS prior to initiation of dopaminergic therapy (DT). B-change in UPDRS due to ST initiation. C-time to initiation of ST. D-trajectory of UPDRS change over time.

accounted for^{30,31}; (3) A potential beneficial effect of isradipine on disease progression could be masked by differential usage of ST. To account for this factor, we will evaluate *differential use of ST* by calculating the levodopa equivalent dosages between treatment groups³²; (4) Incidence and severity of nonmotor symptoms, as these contribute disproportionately to quality of life and reflect clinically relevant outcomes in PD.^{33–35}

A variety of *exploratory outcome measures* will be evaluated including global measures of functional disability measured by the modified Rankin scale,³⁶ quality of life measured by PDQ-39³⁷ and NeuroQOL,³⁸ the change in the ambulatory capacity (sum of 5 UPDRS items: falling, freezing, walking, gait, postural stability)³⁹, and cognitive function as measured by MOCA.²⁴ Finally, we will model the trajectory of UPDRS change before and after initiation of ST (D in Fig. 2).

Plasma pharmacokinetic (PK) samples will be collected at the screening, 3 month and 6 month visits. The objective of collecting blood PK samples is to confirm isradipine trough concentrations and to establish a sparse PK profile of isradipine in this population. In addition, blood samples to extract DNA will be collected at screening and plasma will be collected at screening and at the end of the study and stored for future unspecified research.

Statistical analyses

Efficacy analyses will use the intent-to-treat principle. The primary analysis will compare the active treatment group (all participants randomized to receive active isradipine)

with the placebo group. All *P*-values for efficacy outcomes will be two-sided.

The primary analysis will use analysis of covariance applied to the change from baseline in the total UPDRS score. The baseline value will also be entered into the model as a continuous variable, the assigned treatment and enrolling site will be entered as categorical variables. A two-tailed test with $\alpha = 0.05$ will be used to declare statistical significance.

Secondary efficacy analyses of continuous outcome measures will be performed similar to the primary analysis. The time to initiation of ST and the time to onset of motor complications will be analyzed using Kaplan–Meier plots and Cox Regression.

Supplementary analyses of the final study outcomes will be conducted with current use of symptomatic medication (levodopa equivalents) added as an additional predictor variable. The purpose of this analysis is to assess whether any differences seen in the primary outcome variable could be attributed to differential use of ST between the treatment groups. We aim to demonstrate that at 36 months participants on isradipine will have less functional decline than participants on placebo, without requiring more ST. We will also perform exploratory analyses of the primary outcome, using quantitative modeling along the lines suggested by Holford and Nutt,⁴⁰ which permits exploration of both short-term symptomatic effects and long-term disease-modifying effects of treatment in order to further evaluate the differential impact of isradipine and ST.

Recognizing that the study does not have high power to detect treatment effects among subgroups, we will conduct exploratory analyses to check the consistency of treatment effects on the primary and secondary efficacy measures in relation to selected baseline characteristics, including gender and race/ethnicity.

Power and sample size considerations

Previous studies^{29,30,41} support a standard deviation of 12.0 units for the change in the primary outcome, total UPDRS from baseline to 36 months. The same data suggest an average change in total UPDRS of around 4.0 points over this same time period. However, this change is deceiving, as the change would likely be much greater in the absence of symptomatic treatment. If we assume that treatment with levodopa or a dopaminergic agonist provides a “bonus” of 12 points, then the underlying true decline in function over this period would be approximately 16 points, a value broadly consistent with the rate of change in total UPDRS in participants prior to treatment. We have chosen to power our study to detect a 4-point effect, representing an overall 25% reduction in the

underlying rate of progression. Using the above assumptions, a two-sided test with $\alpha = 0.05$ and $\beta = 0.8$ and making allowance for 15% dropouts, the required sample size is 168 participants per group or a total 336 participants.

We are also sufficiently powered to address our key secondary outcomes. Given the sample size above, we will be able to detect a 29% reduction in the risk of initiating ST; a reduction of 40% in the risk of developing motor complications; an approximately 25% reduction in the dosage of ST; and an effect size of 1.5 points on the non-motor experiences of daily living between treatment groups.

Interim analyses

An interim analysis for futility and efficacy will be performed after primary outcome data are available for the first 168 participants (50%) to enroll. The study will be terminated for futility if the interim analysis shows that the conditional power of rejecting the null hypothesis in favor of a beneficial effect of isradipine is lower than 20% under any scenario that is consistent with the data accrued at that time. A two-sided *P*-value in favor of isradipine of less than 0.001 will be required to stop for efficacy at the interim analysis. The stringent alpha level for efficacy was chosen so as to have minimal effect on the final *P*-value, should the study run to completion. In addressing futility, the DSMB will examine a range of possible treatment effects consistent with the data obtained in the study at the time of analysis.

Results

Enrollment of the 336 participants began in November 2014 and was completed in October 2015 at 55 of the 57 active PSG sites. The final subject is expected to complete the study in November 2018. Baseline characteristics of the enrolled cohort are detailed in Table 2. At the time of this report, 330 participants remain active in the study with 322 participants on active drug.

Discussion

STEADY-PDIII is a novel PD disease-modifying trial evaluating efficacy of isradipine compared with placebo over 36 months. Several novel aspects of study design can be highlighted. It is the longest duration disease modifying trial ever conducted in de novo PD. In addition, the primary outcome (UPDRS change in the practically defined ON state) is powered to detect a 25% slowing of functional decline with isradipine above the benefit from ST,

Table 2. Baseline characteristics of the enrolled cohort.

Enrolled cohort (<i>n</i> = 336)	Value ¹
Age	61.9 (9.0)
Male gender, <i>n</i> (%)	230 (68.5)
White, non-Hispanic, <i>n</i> (%)	300 (89.3)
Years from diagnosis	0.9 (0.7)
Hoehn and Yahr Stage	1.7 (0.5)
Schwab and England ADL score	94.0 (7.9)
Total UPDRS	23.1 (8.6)
Mental UPDRS	0.7 (1.1)
ADL UPDRS	5.2 (3.1)
Motor UPDRS	17.2 (7.0)
MDS-UPDRS Total	32.4 (11.6)
MoCA	28.1 (1.4)
Amantadine use at baseline, <i>n</i> (%)	20 (6.0)
Anticholinergic use at baseline, <i>n</i> (%)	5 (1.5)

ADL, activities of daily living; UPDRS, Unified Parkinson Disease Rating Scale; MDS, Movement Disorders Society; MoCA, Montreal Cognitive Assessment.

¹Values represent mean (standard deviation) unless otherwise specified.

a difference that would be sufficient to influence clinical practice and may suggest the likelihood of longer term benefit. Finally, we are looking at a variety of relevant motor and nonmotor outcomes that will serve to support the effect of isradipine on outcomes that are clinically relevant to patients and clinicians.

PD is a slowly progressive neurodegenerative disease. Most of the previously conducted disease-modifying studies enrolled participants with newly diagnosed PD not yet requiring ST and followed them for a relatively short period of time (12–24 months) assuming that if benefit is shown it will persist long term.⁴² In case the participant required initiation of ST, the last observation prior to symptomatic treatment was carried forward. Such design is driven by lack of objective biomarkers of PD progression and the significant impact of ST on standard clinical outcome measures. However, this design is artificial and does not address “real life scenarios” where all patients are ultimately treated with ST. Indeed, on average 50% of de novo PD patients initiate ST within 1 year⁴³ with nearly 100% requiring therapy by 3 years.^{44,45} If the effect of isradipine on progression influences the rates of initiation of therapy, then we will be able to evaluate this through our key secondary outcome measures looking at time to initiation of ST and differential use of ST. Even if an intervention is effective early in the course of the disease, it remains to be proven that the benefit will persist longer term and specifically after initiation of ST. The interpretation of previous disease-modifying therapies has been obscured by this lack of long-term follow-up.

STEADY-PDIII attempts to address these limitations through 36-month follow-up of a randomized and blinded cohort. At 36 months, nearly all participants are expected to be treated with symptomatic therapies; therefore, this study is powered to demonstrate a disease-modifying effect, if such exists, “on top of” the symptomatic benefit of existing treatments, making the results more clinically relevant and reflecting a “real life scenario” in a relatively small cohort of patients. Although we recognize that 36 months is not a substantially long period to see the emergences of long-term complications such as postural instability and dementia, it is the longest duration ever proposed for a study in a de novo untreated PD population and is likely long enough to provide insight into the effect of isradipine on relevant motor and nonmotor outcomes. It is also a practically feasible time to maximize participant retention. Thus, the study design is novel in that it allows us to take advantage of a relatively small cohort to address the longer duration benefits of isradipine on top of the benefit derived from ST and to address clinically relevant longer duration motor and nonmotor outcomes.

We considered alternative study designs including a “simple long duration study” design (LS-1), but this design would require in excess of 1500 participants and 7–8 years to complete.³⁹ Another design used in PD neuroprotective trials is the delayed-start design.⁷ The arguments against a delayed-start design are the lack of demonstrable symptomatic benefit of isradipine, the requirement of >1000 participants for sufficient power, and controversy on its ability to demonstrate disease modification in PD. Another consideration would be to enroll individuals at the time of initiation of symptomatic therapy (e.g., CALM-PD),³⁰ however, this would not allow us to evaluate the impact of isradipine on progression early in disease not confounded by symptomatic therapy, would not allow us to assess the impact of isradipine on the timing of initiation of ST and would be unlikely to add value as both scenarios would assess baseline UPDRS prior to the initiation of symptomatic therapy. In addition, enrolling participants as early as possible in the disease process would allow us to maximize the neuroprotective benefit of isradipine if such an effect exists. We also considered a prolonged wash out at the end of study or at the time of initiation of ST to reassess for the evidence of symptomatic benefit, but there are strong arguments against such design, including lack of obvious symptomatic effect of isradipine in our Phase II STEADY-PD2 study and participant burden. In addition, there is no consensus regarding the necessary duration of the washout that would be required for isradipine.^{5,28} Therefore, our design represents the most rational approach to study the efficacy of isradipine on disability in PD.

Our primary outcome is the change in UPDRS in the practically defined “ON” state from baseline to 36 months. Despite its limitations, UPDRS remains the best characterized outcome measure in PD and motor UPDRS correlates with neuronal loss in the substantia nigra.⁴⁶ In addition, substantial data exist on the rate of change in the UPDRS in the de novo PD population and on the clinical meaningfulness of this outcome to allow us to adequately power this study. We have chosen to evaluate UPDRS in the medication “ON” state once ST is initiated, which will allow us to identify the benefit of isradipine “on top of” the benefit conferred by ST, an outcome with “real world” relevance to patients and clinicians. We have carefully considered UPDRS “OFF” as an alternative primary outcome. While it may be argued that the “OFF” assessment is a better representation of dopaminergic deficit this is not supported by the clinical data (31–33).^{47–49} Both levodopa and dopamine agonists have shown long duration effects on UPDRS lasting days and even weeks, so that traditional 12 h off medication assessment does not reflect true dopaminergic deficiency. Despite these limitations, we recognize the potential value of “OFF” assessments and the motor UPDRS will be assessed as an exploratory outcome in the defined medication “OFF” state (at least 12 h after last dose of ST) once ST has been initiated.

In addition, we have identified a number of key secondary outcomes to corroborate the findings from the primary analysis. These outcomes include time to initiation of ST, time to the development of motor complications, use of ST and nonmotor disability. Time to initiation of ST has been a primary outcome in several completed studies that examined the efficacy of putative disease-modifying interventions.^{5,29} Although it has been criticized for the subjective nature of the measure and being impacted by the change in the treatment algorithms that overall lead to the earlier initiation of ST, nevertheless it can be considered a surrogate measure of the disease progression and allows us to compare our findings with previous trials. The differential use of ST has the potential to obscure the results and may represent a surrogate of disease severity. For instance, individuals with greater progression may be on higher dosages of ST which may offset the benefit of slower progression as measured by the UPDRS. Not only will this serve as a surrogate of disease progression and severity, it will allow us to conduct exploratory analyses accounting for ST effects.

The development of motor complications represents a significant milestone in PD progression and results in impaired quality of life, function, and social isolation.⁵⁰ Therapies aimed at preventing or ameliorating motor complications represent a major unmet therapeutic need

in PD. If isradipine only resulted in a difference in the rate of motor complications, this would represent a clinically meaningful outcome that would likely influence care. Nonmotor symptoms can be challenging to treat and have a disproportionate impact on quality of life.^{51–53} Therefore, therapy that influences these outcomes will likely have a significant impact on PD quality of life. The MDS-UPDRS evaluated a variety of nonmotor outcomes not assessed in the traditional UPDRS. STEADY-PD III represents the first interventional trial in de novo population to systematically evaluate the MDS-UPDRS and will allow for further validation of this scale. We have chosen not to use it as the primary outcome as there were limited data on the change in MDS-UPDRS in de novo PD to power the study. We have also chosen a number of exploratory measures that take advantage of the longer duration of follow-up in this study compared with previous de novo studies and represent clinically valuable and complementary outcomes in PD. These measures represent components of the NINDS Common Data Elements and have largely been validated in PD and include measures of function, quality of life, gait, and cognition.

The study design has some limitations. A biomarker to validate target engagement of isradipine at the CAV1.3 channel does not exist and therefore a negative study may reflect a failure of target engagement. We have considered collecting biomarkers of oxidative stress and mitochondrial function as potential downstream effects of isradipine but these would only be indirect measures and have not been validated with isradipine in *in vivo* or *in vitro* models. We are collecting DNA and plasma for future analyses of novel biomarkers that may assist in interpretation of the study. We will analyze PK data to ensure that a minimum concentration necessary for neuroprotection is achieved and to address whether variability in clinical response is related to variations in serum concentrations. A final limitation is that participants are enrolled based on the clinical diagnosis of PD, raising the possibility that approximately 10% of participants might not have a presynaptic dopaminergic deficit. The use of DAT scan at enrollment could obviate this concern but would be associated with increased costs and time and would not definitively exclude individuals without PD. All investigators are credentialed by the PSG, experienced in the diagnosis and care of PD and the conduct of PD-related trials and therefore, we anticipate a low false-positive diagnosis rate. Regardless, we are collecting data on the change in diagnosis and will conduct post hoc analyses that incorporate this information.

In conclusion, this study is testing isradipine as a potential novel neuroprotective agent in PD based on robust preclinical and strong epidemiological data. The STEADY-PDIII study design is unique in assessing the

impact of isradipine over 36 months, at a time point where all participants will likely be on ST allowing us to determine if the benefit is sustained “on top of” traditional ST. In addition, the study design allows us to determine if the effects on motor function are corroborated by important secondary outcomes assessing clinically relevant measures of ST use, motor complications, nonmotor function, global disability, quality of life, ambulatory capacity, and cognition. This design is novel and innovative and allows for the determination of longer duration benefits on several clinically relevant outcomes in a relatively small cohort on top of the benefit derived from ST.

Conflict of Interest

None of the authors have relevant conflicts of interest.

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