A Phase 3 double-blind placebo-controlled parallel group study of isradipine as a disease modifying agent in subjects with early Parkinson disease

Acronym:	STEADY-PD III (**S**afety, **T**olerability, and **E**fficacy **A**ssessment of **Isradipine** for **PD**)
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Biomarker and DNA sample collection substudy
Supported by Michael J. Fox Foundation

INVESTIGATOR AGREEMENT

I have carefully read this protocol, including all appendices and the isradipine Package Insert and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current Good Clinical Practice (GCP) regulations and guidelines [21 CFR (Code of Federal Regulations) Parts 11, 50, 54 and 56 and ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) Topic E6 (R1)], and local regulatory requirements. Any changes in procedure will only be made if necessary to eliminate immediate hazards and/or to protect the safety, rights or welfare of subjects.

I will provide copies of the protocol and all other information relating to the pre-clinical and prior clinical experience, which were furnished to me, to all physicians and other study personnel responsible to me who participate in this study. I will discuss this information with them to assure that they are adequately informed regarding the study drug and conduct of the study.

I will ensure that the drugs supplied to me for this study will be used only for administration to subjects enrolled in this study protocol and for no other purpose.

I agree to keep records on all subject information (case report forms, informed consent statements, drug shipment, drug return forms, and all other information collected during the study) in accordance with the current GCP, local and national regulations.

Site Number	Printed Site Name

Printed Site Investigator Name

Site Investigator Signature	Date

PROTOCOL APPROVAL

A Phase 3 double-blind placebo-controlled parallel group study of isradipine as a disease modifying agent in subjects with early Parkinson disease

STUDY ACRONYM: STEADY-PD III

10/14/2016

Tanya Simuni
Principal Investigator

Date

10/7/16

Kevin M. Biglan
Co-Principal Investigator

Date

Oct 6, 2016

David Oakes
Biostatistician

Date

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol Version 1.0	6January2014	Not applicable
Version 2.0	11March14	• Revised information related to collection of home blood pressure monitoring to remote internet uploading and home BP readings, oversight and site responsibility with review of BP readings • Clarified drug titration requirements • Added requirement to report re-initiating blood pressure monitoring after Visit 02 • Clarified management of subject's who become pregnant • Changed biomarker serum sample to plasma sample • Changed reporting of SBP from 140 to 160 mm Hg • Added information on reporting of SAEs to Independent Medical Monitor • Added responsibility of Blood Pressure Monitor • Clarified Investigator training requirements for UPDRS, MDS-UPDRS and C-SSRS • Clarified assessment roles for Investigator and Coordinators for UPDRS and MDS-UPDRS • Clarified processing of AE Incident Reports
Version 3.0	09May14	• Revised Kevin Biglan's title • Added Michael J. Fox Foundation as sponsor of biomarker sub-study • Updated Abbreviation Terms to include ADL, DNA and Neuro-QOL • Revised inclusion criteria to allow PD symptomatic therapy after 3 months from the baseline visit • Revised exclusion criteria to include ALL calcium channel blockers • Clarified definition of medication ON state • Changed blood pressure collection from supine to sitting position • Added optional DNA collection at Screening visit • Added Neuro-QOL measures to be assessed at Baseline, Month 12, Month 24, Month 36 or PW visit and at Symptomatic Treatment Visit • Added Neuro-QOL to study measures for quality of life • For interim PK analysis, clarified DSMB response to seek

Document	Date of Issue	Summary of Change
		independent assessment • Removed statement to terminate study for futility if interim analysis shows conditional power of rejecting null hypothesis • Clarified procedures to be completed at Symptomatic Treatment Visit, to include Symptomatic Treatment Visit replacing regularly scheduled visit, as applicable, and added collection of labs and ECG if this visit occurs at V06, V08 or V10 • Revised plan to withdraw subject if treatment assignment has been disclosed to retain subject off of study drug • Corrected name for Drug Dispensing/Return Log and Blindedness Questionnaire throughout • Clarified BP Monitor communication with Site Investigator • Referenced Section 3 of Operations Manual to add guidance to requirements for eligibility waiver process • Changed follow up of adverse events from 2 weeks after stopping study drug to 30 days from last visit or until resolution, whichever occurs first • Clarified Data Sharing in Section 11
Version 4.0	15Dec14	• Change in use of amantadine and/or anticholinergics from 12 week prior to the baseline visit to 8 weeks prior to baseline visit • Changed primary care physician to primary care provider throughout • Added use of telithromycin to prohibited drug use in exclusion criteria per isradipine package insert • Added association with heart injury to use of prohibited antibiotics in exclusion criteria per isradipine package insert • Added the following to data collection: PD Features at Screening Visit Primary Diagnosis at Screening Visit, V11 and PW Socio-Economics at Screening Visit Family History at Screening Visit Mini Environmental Risk Questionnaire (MERQ) at Baseline Exercise Questionnaire at Baseline, V11 and PW

	• Changed temperature range for storage of study drug due to current manufacturer recommendations • Added instruction to hold study drug if dose missed for 4 hours or more from scheduled time and resume at next scheduled dosing time • Remove instructions for subject to report blood pressure to site personnel • Added instruction to continue birth control for two weeks after study drug has been discontinued • Added information on prohibited use of Fentanyl Anesthesia • For MoCA, added information on addition of point for education of 12 years or fewer • For Neuro-QOL assessments, added information on available translation; French-speaking participants not expected to complete • Revised Study File and File Document list • For EDC Electronic Signature requirements, added AE Follow up Log • For Adverse Events, included information on phone call management for AEs present at V10 or PW visit • Added the following for reportable events: Re-initiation of BP monitoring at V02 Completion of DaT Scan • Other minor formatting and language revisions for consistency and clarification

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Version 6.0	31AUG2016	• Removed the remote blood pressure monitoring for study visits during a study drug taper and at the end of the study • The Telephone Visit T01, T02, T03, or T04 may be conducted by either the study coordinator or investigator • Visit windows beginning T01 Month 15 through V10 Month 36 revised from +/- 14 days to +/- 7 days • Added additional description for the UPDRS “ON” and “OFF” that should occur for all types of PD medications once a symptomatic therapy visit is conducted

	• Obtain consent for study principal investigator or representatives to contact subject for long term follow up after study (36 months) completion • Added at the V10 End of Study Visit to review informed consent and verify that the subject granted permission for long term DNA and biomarker storage • Added a description of blanket retention methods including a subject webinar with study principal investigators • Revised the Schedule of Activities footnotes to indicate collection of MERQ, Exercise Questionnaire, DNA and Biomarker samples at the next in-person visit if missed at the Baseline visit • Added the visit status assessment to be completed at all visits • Schedule of Activities - Added a Premature Withdrawal Follow-Up Visit • Schedule of Activities - Deleted the "X" for Home BP Monitoring • Protocol Section 6.2 deleted reference to remote phone visits • Protocol Section 9.2.5 revised data entry requirement revised to 5 days • Protocol Section 10.2 added a timeline to retention of subject contact information (20 years) • Formatting and language revisions for consistency and clarification

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Abbreviations or Specialist Terms

Abbreviation or Specialist term	Definition
ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BDI-II	Beck Depression Inventory II
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CCB	Calcium Channel Blockers
C_{max}	Maximum Observed Plasma Concentration
CMSU	Clinical Materials Services Unit
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CTCC	Clinical Trials Coordination Center
DCCA	Dihydropyridine Calcium Channel Antagonist
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOSD	End of Study Drug
GCP	Good Clinical Practice
HTN	Hypertension
ICH	International Conference on Harmonisation
ID	Identification
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase

MERQ	Mini Environmental Risk Questionnaire
MDS-UPDRS	Movement Disorder Society- Unified Parkinson Disease Rating
MoCA	Montreal Cognitive Assessment
MODHOYA	Modified Hoehn and Yahr
MODSEADL	Modified Schwab and England Activities of Daily Living
mRS	Modified Rankin Score
Neuro-QOL	Quality of Life in Neurological Diseases
NINDS	National Institute of Neurological Disorders and Stroke
OFF	Approximately 12 hours after the last dose of symptomatic therapy
ON	Approximately 1 hour after dose of symptomatic therapy
PD	Parkinson disease
PDQ39	Parkinson Disease Quality of Life Questionnaire
PI	Principal Investigator
PK	Pharmacokinetics
PSG	Parkinson Study Group
PTM	Placebo to Match
REB	Research Ethics Board
RBC	Red Blood Cell
SAE	Serious Adverse Event
SD	Standard Deviation
STX	Symptomatic therapy
UPDRS	Unified Parkinson Disease Rating Scale
URT	Upper Respiratory Tract
WBC	White Blood Cell
WO	Without

SYNOPSIS

Protocol Title	**A Phase-3 double-blind placebo-controlled parallel group study of isradipine as a disease modifying agent in subjects with early Parkinson disease**
Protocol Acronym	STEADY-PD III
Organization	Parkinson Study Group (PSG)
Study Centers	Approximately 56 PSG sites in North America
Primary Study Objective	To establish efficacy of isradipine to slow progression of Parkinson disease (PD) disability as determined by the change in the total (Part I-III) Unified Parkinson Disease Rating Scale (UPDRS) score in the active treatment arm versus placebo between the baseline and 36 month visit
Secondary Study Objective	To explore long-term efficacy of isradipine 5 mg twice daily to slow progression of disability between baseline and 36 months of treatment as measured by parameters that reflect long term disability in PD: 1) Motor function (characterized by UPDRS Part III in the medications OFF state, UPDRS ambulatory capacity subscore, time to initiation of symptomatic therapy, time to onset of motor complications, dosage and utilization of symptomatic therapy, MDS-UPDRS Motor score) 2) Cognitive function as measured by the Montreal Cognitive assessment Scale (MoCA) 3) Global measures of disability as measured by modified Rankin score 4) Measures of functional status and quality of life (PDQ-39, MDS- UPDRS Motor and Non-Motor Experience of Daily Living)
Study Design	A randomized, Phase-3, 2-arm, double-blind, parallel group trial with subjects 1:1 randomized to 5mg of Isradipine IR twice daily or matching placebo twice daily.
Duration of Treatment	36 months on randomized treatment of 5mg of Isradipine IR twice daily or matching placebo.
Route and Dosage	Oral capsules Isradipine IR or matching placebo

Study Population	336 subjects with early idiopathic PD not requiring dopaminergic therapy
Study Inclusion Criteria	1. Subjects with early idiopathic PD (presence of at least two out of three cardinal manifestations of PD). If tremor is not present, subjects must have unilateral onset and persistent asymmetry of the symptoms 2. Age equal or greater than 30 years at the time of diagnosis of PD 3. Hoehn and Yahr stage less than or equal to 2 4. Diagnosis of PD less than 3 years. 5. Currently NOT receiving dopaminergic therapy (levodopa, dopamine agonist or MAO-B inhibitors) and NOT projected to require PD symptomatic therapy for at least 3 months from the baseline visit 6. Use of amantadine and/or anticholinergics will be allowed provided that the dose is stable for 8 weeks prior to the baseline visit **7.** If subject is taking any central nervous system acting medications (e.g., benzodiazepines, antidepressants, hypnotics) regimen must be stable for 30 days prior to the baseline visit 8. Women of childbearing potential may enroll but must use a reliable measure of contraception and have a negative serum pregnancy test at the screening visit
Study Exclusion Criteria	1. Subjects with a diagnosis of an atypical Parkinsonism 2. Subjects unwilling or unable to give informed consent 3. Exposure to dopaminergic PD therapy within 60 days prior to baseline visit or for consecutive 3 months or more at any point in the past 4. History of clinically significant orthostatic hypotension or presence of orthostatic hypotension at the screening or baseline visit defined as greater than or equal to 20 mmHg change in systolic BP ***and*** greater than or equal to 10 mmHg change in diastolic BP from sitting position to standing after 2 minutes, or baseline sitting BP less than 90/60 5. History of congestive heart failure 6. Clinically significant bradycardia 7. Presence of 2nd or 3rd degree atrioventricular block or other significant ECG abnormalities that in the investigator's opinion would compromise participation in study 8. Clinically significant abnormalities in the Screening Visit laboratory studies or ECG 9. Presence of other known medical or psychiatric comorbidity that in the investigator's opinion would compromise

	participation in the study 10. Prior exposure to isradipine or other dihydropyridine calcium channel blockers (see list in Operations Manual) within 6 months of the baseline visit 11. Subjects on greater than 2 concomitant antihypertensive medications. If a history of hypertension, then a maximum of 2 other antihypertensive agents will be allowed provided that the dosages of concomitant anti HTN therapy can be reduced/adjusted during the study based on the BP readings in consultation with the subject's primary care provider or cardiologist. Use of any concomitant calcium channel blockers will not be allowed from the baseline visit and for the duration of the study 12. Use of grapefruit juice, ginkgo biloba, St. John's wort or ginseng will be prohibited starting from the screening visit and for the duration of the study (as they interfere with the metabolism of isradipine) 13. Use of clarithromycin, telithromycin and erythromycin will be prohibited starting from the screening visit and for the duration of the study as the combination of clarithromycin, telithromycin or erythromycin and calcium channel blockers has been reported to be associated with increased risk of kidney and heart injury 14. Presence of cognitive dysfunction defined by a Montreal Cognitive assessment (MoCA) score of less than_26 at screening 15. Subjects with clinically significant depression as determined by a Beck Depression Inventory II (BDI) score greater than 15 at the screening visit 16. History of exposure to typical or atypical antipsychotics or other dopamine blocking agents within 6 months prior to the baseline visit 17. History of use of an investigational drug within 30 days prior to the screening visit 18. History of brain surgery for PD 19. Allergy/sensitivity to isradipine or its matching placebo or their formulations 20. Pregnant or lactating woman
Primary Outcome Measure	**Efficacy:** Efficacy will be defined as the change in total UPDRS score between the baseline visit and month 36 visit. In case the subject was started on symptomatic therapy, UPDRS will be measured in the medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy).

Secondary Outcome Measures	The change in the following measures of disability from baseline to 36 months will be analyzed: I. <u>Motor disability</u> 1. The change in Motor subscale of the UPDRS 2. The change in the ambulatory capacity (sum of 5 UPDRS questions: falling, freezing, walking, gait, postural stability) 3. The change in the defined UPDRS Part III OFF state (measured approximately 12 hours after the last dose of medications) once symptomatic therapy has been initiated 4. The change in the MDS-UPDRS Motor Evaluation subscore 5. The time to initiation of symptomatic therapy 6. Proportion of subjects that require symptomatic therapy 7. Analysis of symptomatic therapy utilization as measured by levodopa equivalence dose[1] 8. Time to onset and severity of motor complications as measured by UPDRS IV subscale (complications of therapy) II. <u>Cognitive disability</u> 1. The change in the cognitive function as measured by the change in the MoCA scale [2, 3] III. <u>Measures of global disability</u> 1. The change in the modified Rankin score IV. <u>Measures of functional status and quality of life</u> 1. The change in Activities of Daily Living (ADL) subscale of the UPDRS 2. The change in the MDS-UPDRS Motor and Non-Motor Experiences of Daily Living subscore 3. The change in the modified Schwab and England scale 4. The change in Parkinson Disease Quality of Life Questionnaire 39 (PDQ-39) [4] 5. The change in the Neuro-QOL **Safety and Tolerability:** 1. The ability to complete the 36 months of the study on the originally assigned treatment dosage. 2. The proportion of subjects requiring dosage reductions secondary to intolerability. 3. The frequency of adverse events and serious adverse events.
Statistical Analysis and Sample Size Justification	The primary efficacy analysis will use analysis of covariance to compare the changes in total UPDRS score from baseline to 36 months between the active treatment group and the placebo group, adjusting for baseline UPDRS and enrolling investigator. Using a

	two-sided alpha level of 5%, the total sample size of 336 gives 80% power to detect a 4–point difference between the two groups, after allowance for 15% dropouts. This effect size is estimated to represent a 25% reduction in the rate of worsening after allowance for the benefit of symptomatic treatment. Secondary outcomes including measures of motor, cognitive and global disability and measures of functional changes and quality of life will be analyzed in the same way as the primary outcome. Measures of safety and tolerability, including ability to complete the study on the assigned dosage and the frequency, seriousness and severity of adverse events will be compared using Fisher's exact test.
Interim Analyses	**Interim tolerability analysis** An interim tolerability analysis will be performed after the first 60 subjects complete the titration period (Visit 03, Month 3). **Interim analysis of the Pharmacokinetic (PK) data** An interim PK data analysis will be performed (at steady-state) after Cmin and Cmax PK data are available for the first 60 subjects who successfully complete titration to the target daily dose of 10 mg (Visit 03, Month 3). **Interim futility and efficacy analysis** An interim analysis for futility and efficacy will be performed after primary outcome data are available for the first 168 subjects (50%) to enroll in the study. If the recruitment rate falls below that projected, the interim analysis may be brought forward and performed as soon as the first 30% of the subjects to enroll have completed (or terminated). In that case, a second interim analysis for futility will be conducted on the first 75% of subjects to enroll.
Study Procedures	See the Schedule of Activities.
IND	The IND application # 113,513

STEADY-PD III Schedule of Activities

		Titration Phase			Maintenance Phase											Drug Taper					
Visits	Screen (SC)	Base-line (BL)	V01	V02	V03	V04	V05	V06	Phone Visit T01 	V07	Phone Visit T02 	V08	Phone Visit T03 	V09	Phone Visit T04 	V10 EOSD	V11 Post drug/ Final Visit	Prema-ture With-drawal (PW)	PW Follow-Up Visit[11]	Unsched sched-uled Visit (U01, U02)[5]	Symp-tomatic Tx Visit
Assessments	-8--30 days	Day 0	Day 14 + 3 days	Day 28 + 3 days	Month 3 +/-7 days	Month 6 +/- 7 days	Month 9 +/- 7 days	Month 12 +/- 7 days	Month 15 +/- 7 days	Month 18 +/- 7 days	Month 21 +/- 7 days	Month 24 +/- 7 days	Month 27 +/- 7 days	Month 30 +/- 7 days	Month 33 +/- 7 days	Month 36 +/- 7 days	Visit10 + 2 weeks		~2 weeks post study drug taper		As soon as deemed neces-sary
Informed Consent	X																				
Incl./Excl Criteria	X	Re-view																			
Demographics	X																				
CTCC Unique ID	X																				
Obtain name of PCP and/or Cardi-ologist	X																				
PD Features	X																				
Primary Diagnosis	X															X		X			
Socio-Economics	X																				
Family History	X																				
Med / Neuro HX	X																				
Physical/Neuro	X															X		X			
Concomitant Medi-cation Log	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS - BL	X																				
C-SSRS Follow-up		X	X	X	X	X	X	X		X		X		X		X	X	X	X		X
BDI-II	X							X				X				X		X			X
MoCA	X							X				X				X		X			X
Vital Signs (including orthos-tatic BP)	X	X	X	X	X	X	X	X		X		X		X		X	X	X	X	X	X
Safety Labs	X	Re-view						X				X				X		X		X^2	X^{13}
Blood Sample for DNA[14 16]	X																				
Plasma Biomarkers [16]	X															X		X			
Pregnancy Test [6]	X							X				X				X		X			X^{13}
Modified Rankin scale		X						X				X				X		X			X
Isradipine PK Sample	X				X	X												X^9			
ECG	X	Re-view						X				X				X		X			X^{13}
PDQ-39		X						X				X				X		X			X
Neuro-QOL		X						X				X				X		X			X
UPDRS (I-III)[3]		X	X	X	X	X	X	X		X		X		X		X	X	X	X (if not done at PW visit)		X
UPDRS IV[1]			X	X	X	X	X	X		X		X		X		X	X	X	X (if not		

																			done at PW visit)			
UPDRS III Post Dose					X[14]	X[14]	X[14]	X[14]		X[14]		X[14]		X[14]		X[14]	X[14]	X[14]			X
MDS- UPDRS[4]		X						X				X				X		X			X
Assess Need for Therapy	X	X	X	X	X	X	X	X	X[7]	X	X[7]	X	X[7]	X	X[7]	X	X	X	X (if not done at PW visit)		
Hoehn and Yahr	X	X	X	X	X	X	X	X		X		X		X		X	X	X	X (if not done at PW visit)		X
Schwab/ England		X	X	X	X	X	X	X		X		X		X		X	X	X	X (if not done at PW visit)		X
MERQ[16]		X																			
Exercise Questionnaire [16]		X															X	X			
Visit Status Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X																			
Dispense/Titrate Drug		X		X		X		X		X		X		X		X					X[13]
Dose Management Log		X	X	X	X	X	X	X		X		X		X		X	X	X	X if not done at PW visit	X[8]	X
Drug Dispensing/Return Log Pill count		X	X	X	X	X	X	X		X		X		X		X	X	X	X (if not done at PW visit)		
Adherence Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[15]	X[15]	X	X	X
Train BP Monitoring	X																				
Home BP Recording[2]	X	X	X	X																	
Review of Home BP Readings [12]		X	X	X	X*																
Blindedness Questionnaire [10]																	X	X	X (if not done at PW visit)		
Conclusion of Study Participation																	X	X	XX		

[1]If endpoint has been reached

[2] During the study drug titration period from BL to V03, blood pressure recording should be re-initiated when a dosage reduction was due to hypotensive symptoms. Home blood pressure monitoring is not required after the V03 for re-titration.

[3]UPDRS motor portion must be completed by the Investigator. Once subject initiated symptomatic therapy, UPDRS Parts 1 and 2 to be completed in the ON state, UPDRS Part III will be assessed in the practically defined medication OFF state (approximately 12 hours since last dose of symptomatic therapy) and ON (approximately 1 hour after first dose of symptomatic therapy). Subjects should be instructed NOT to take their PD med-

ications at home on the morning of the study visit. Subjects should be instructed to bring their PD medication to the study visit. Medication should be taken after completion of UPDRS OFF exam.

[4]Once symptomatic therapy has been initiated, MDS-UPDRS in the medication ON state only

[5] If an Unscheduled visit is scheduled to reduce antihypertensive medications, the visit should include all V01 procedures and evaluations

[6] Complete serum pregnancy test for all women unless they are one year postmenopausal or surgically sterile

[7] If a subject reports functional decline requiring symptomatic treatment an Unscheduled visit should be scheduled

[8] Dose management is completed at Unscheduled visit if study drug adjustment is required at the time of this visit

[9] PK sample collection at Premature Withdrawal visit to occur ONLY if visit corresponds to Visits 3 or 4

[10] Blindedness Questionnaire completed by both subject and Investigator

[11] All subjects who **are taking study drug** at Premature Withdrawal visit must have Premature Withdrawal Follow Up visit scheduled to occur 2-weeks after drug has stopped. Subjects who withdraw consent should be asked to agree to present for this visit.

[12] Site staff will access BP vendor website to obtain confirmation notice to proceed or not proceed with drug titration. This confirmation along with review of in-person readings will be used to proceed or not proceed with drug titration per study BP requirements.

[13]If the symptomatic treatment visit occurs within the window of a regularly scheduled study visit, the symptomatic treatment visit will be completed in place of the regularly scheduled study visit. If this visit is conducted in place of the regularly scheduled V06, V08 and V10, visit assessments will include the following additional assessments: safety labs, pregnancy test[6], ECG, drug dispensing/titration.

[14]If indicated for Symptomatic Therapy.

[15]Follow up of any unresolved Adverse Events or SAEs must be conducted by phone call, 30 days after the final study visit (Visit 11 or Premature Withdrawal Follow Up visit).

[16] Once subject has provided consent, conduct/collect at the next in-person visit.

1 STUDY OBJECTIVES

1.1 Primary Objective

To establish efficacy of isradipine to slow progression of Parkinson disease (PD) disability as determined by the change in the total UPDRS score in the active treatment arm versus placebo between baseline and 36 months in the medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy). We hypothesize that isradipine 5 mg BID will result in a 4 point difference in the change in total UPDRS between the active and placebo groups over 36 months, representing an overall 25% reduction in the rate of progression.

1.2 Secondary Objectives

To explore long-term efficacy of isradipine 5 mg twice daily to slow progression of disability between the baseline and 36 months of treatment as measured by parameters that reflect long term disability in PD:

1) Motor function (characterized by UPDRS Part III in the medications OFF state, UPDRS ambulatory capacity subscore, time to initiation of symptomatic therapy, time to onset of motor complications, dosage and utilization of symptomatic therapy, MDS-UPDRS Motor score)

2) Cognitive function as measured by MoCA

3) Global measures of disability as measured by modified Rankin score (mRS)

4) Measures of functional status and quality of life (PDQ-39, MDS- UPDRS Motor and Non-Motor Experiences of Daily Living subscore)

1.3 Study Population

The study will recruit 336 subjects with early PD not requiring dopaminergic therapy (levodopa, dopamine agonist or MAO-B inhibitors) and NOT projected to require PD symptomatic therapy for at least 3 months from baseline. Use of amantadine and/or anticholinergics will be allowed provided that the dose is stable for 8 weeks prior to baseline visit and throughout the duration of the study (see Section 4.1 and 4.2 Inclusion/Exclusion criteria). Subjects will be randomized in equal numbers to isradipine 5mg twice daily or matching placebo. Study duration is 36 months. Primary efficacy analysis will be performed after all subjects complete 36 months on their randomized treatment assignment. All subjects who start symptomatic therapy will continue in the study and remain on their randomized treatment assignment (see rationale section below).

2 BACKGROUND

2.1 Rationale and Supporting Data

Parkinson disease (PD) is the second most common neurodegenerative disease that affects 1% of the population above the age 65 [5]. The prevalence of PD will increase substantially in

the next 20 years due to the aging of the population and age-related increase of the incidence of the disease [6, 7]. PD is characterized by progressive motor disability that includes bradykinesia, rigidity, resting tremor and gait dysfunction. PD is associated with a spectrum of non-motor symptoms including autonomic, cognitive, mood, sleep dysfunction and sensory abnormalities which are intrinsically related to the widespread PD neuropathological process and can in part precede the onset of motor manifestations [8]. The economic burden of PD is estimated to be $23 billion annually in US and projected to increase to $50 billion by year 2040 [9]. Most of the cost is due to lost productivity and correlates with more advanced stages of the disease signifying the importance of developing treatment strategies that slow progression of accumulating disability [10].

Treatment options for PD are limited to symptomatic therapy geared towards replacement of dopamine deficiency [11]. Despite a wide armamentarium of effective symptomatic therapy for early PD, management of advanced disease is limited. Availability of an effective disease modifying intervention that will slow the progression of the disease will have a substantial impact on the patients' quality of life and the economic burden of disease.

As of today there is no single proven neuroprotective agent in PD [12]. Tested agents targeted various potential mechanisms of PD pathogenesis including oxidative stress (rasagiline, selegiline, Vitamin E), mitochondrial dysfunction (CoQ10, creatine), apoptotic mechanism of cell death (caspase inhibitors) and others [13-21].

The principal motor symptoms of PD are attributable to the preferential loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc). The selective vulnerability of DA SNc neurons may lend important clues to the etiology of PD. Data from the laboratory of Surmeier suggest that this selective vulnerability may be due to the reliance of these neurons on L-type $Ca_v1.3$ Ca^{2+} channels [22]. This research has shown that adult SNc DA neurons have a very distinctive physiology in that they are Ca^{2+}-dependent autonomous pacemakers [22]. That is, their basal activity is intrinsically generated and dependent upon a particular class of voltage-dependent L-type Ca^{2+} channels. The reliance upon Cav1.3 channels grows with age, paralleling the increasing sensitivity to toxins, like MPTP and rotenone. More importantly for PD, their work shows that pretreatment of SNc DA neurons with *isradipine*, a potent dihydropyridine antagonist of L-type Ca^{2+} channels (DCCA), protects these neurons in *in vitro* and *in vivo* models of Parkinsonism.

There are a number of regions of the brain that have cell loss paralleling that of the SNc [8, 23-26]. Although the available data set is fragmented, neurons in the dorsal motor nucleus of the vagus (DMV), locus ceruleus (LC), raphe nuclei (RN), pedunculopontine nucleus (PPN), lateral hypothalamus (LH), tuberomammillary nucleus, basal forebrain (BF) and olfactory bulb all are slow pacemakers like SNc DA neurons. DMV cholinergic neurons, which are thought to be among the earliest neurons with α-synuclein in PD, are spontaneously active [27]; this activity is autonomously generated and depends upon L-type calcium channels (J. Surmeier, unpublished observations). Serotonergic neurons in the RN have broad spikes and are calcium-dependent autonomous pacemakers [28]. This is also true of PPN cholinergic neurons [29]. Perhaps the neurons most affected in PD other than SNc DA neurons are LC noradrenergic neurons [23]. Like SNc DA neurons, they are autonomous pacemakers (with

broad spikes) that engage L-type calcium channels [30]. These neurons display all the signs of mitochondrial oxidant stress found in SNc DA neurons and this stress is significantly alleviated by isradipine. **Taken together, these studies make a compelling case that isradipine should be broadly effective in slowing the progression of PD.**

Pharmacokinetic studies using MPTP treated mice have revealed that subcutaneous administration of isradipine 3mg/day, which is the dosage shown to be neuroprotective [31] achieves a serum concentration of isradipine of ~1 ng/ml (Dr. Surmeier personal communication). Additional studies were performed using an intrastriatal 6-OHDA injection model in which there is progressive loss of dopaminergic terminals and cell bodies in the SNc. The degree of neuroprotection of terminals and cell bodies was determined 3-4 weeks after the insult [32]. These studies show a clear dose-dependence to the protection afforded to both terminals and cell bodies by isradipine. The half-maximal protection of terminals was about 7 ng/ml, whereas it was 5 ng/ml for cell bodies. This serum concentration is above that achieved in humans with FDA approved dosages of isradipine (1-3 ng/ml), but is nevertheless very close.

To estimate the proportion of channels antagonized by isradipine as a function of isradipine concentration, a model was constructed based upon the work of Bean (Bean 1984) [33]. The Bean model assumes that channel antagonism is dependent upon membrane potential with the highest affinity achieved when the membrane is depolarized. To estimate the average membrane potential of a dopaminergic neuron, recordings were made during pacemaking (Fig. 1A inset) and an all-points histogram of membrane potential assembled (Fig. 1A).

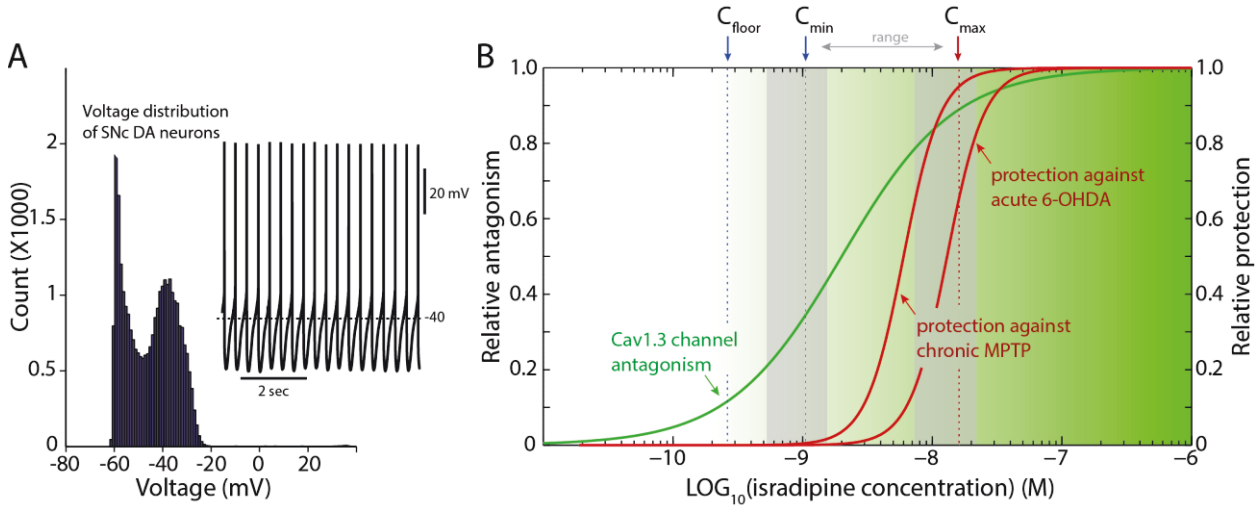

Figure 1.

Neuroprotection is graded over a range of isradipine concentrations that antagonize Cav1.3 calcium channels in pacemaking neurons. A. An all points histogram showing the bimodal distribution of membrane potential in a pacemaking substantia nigra (SN) dopaminergic neuron. Note the inflection point at ~-50 mV. Inset is a representative recording from a pacemaking neuron. B. Three plots are overlaid that illustrate that protection of

SN dopaminergic neurons is graded with Cav1.3 antagonism. First, the green line is a plot of Cav1.3 antagonism as a function of isradipine concentration predicted from a modulated receptor model (Bean 1984), assuming a mean membrane potential of -50 mV. Second, the dose-response relationship for serum isradipine concentration and protection of SN dopaminergic neurons against an acute intrastriatal 6-OHDA injection derived from Ilijic et al.(Ilijic, Guzman et al. 2011) [32], is shown in red. Adjacent is a similar plot extrapolated from earlier work (Chan, Guzman et al. 2007) [31] using a chronic MPTP model. Note the alignment of the protection and Cav1.3 channel antagonism relationships. At the top, the dotted lines mark the estimated serum Cmax and Cmin values for 5 mg twice daily dose of Isradipine IR (Holmes and Kutz 1993) [40]. Cmax serum concentration was 5.5±2.8 ng/ml (14.3 nM+7.5); Cmin concentration was 0.4±0.2 ng/ml (1.1 nM±0.5); grey boxes show the upper and lower limits of the Cmax and Cmin distributions. Note that these are within the range predicted for toxin protection. Also shown is the 'C floor'; this is the value below which there should be little antagonism of Cav1.3 channels and no protection.

This model was used to predict antagonism of Cav1.3 channels as a function of isradipine concentration (Fig. 1B, green line). Plots of the relationship between serum isradipine concentration and neuroprotection achieved against the toxins 6-OHDA and MPTP (Fig. 1B red lines) revealed the graded relationship between channel antagonism and protection. To relate this work to the clinical trial using 10 mg/day Isradipine IR, the Cmax and Cmin values were plotted (Fig. 1B, dashed vertical lines). From these data, we predict that at Cmax roughly 90% of the Cav1.3 channels will be antagonized; at Cmin, this value will fall to just above 30%. Importantly, this range spans the one needed for protection against the toxins. Also plotted is the 'Cfloor' value (0.25 nM or 0.098 ng/ml); at this concentration, Cav1.3 channel antagonism is predicted to be roughly 10%. Although less than that needed to achieve protection against MPTP, this level of antagonism should still provide some measure of protection against the slowly progressing pathology in PD. However, if isradipine concentration falls below this level for part of the day, little or no protection should be afforded during this period.

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2.2 Isradipine Clinical Experience

The study will utilize Isradipine immediate release preparation. Currently there are no $Ca_v1.3$ Ca^{2+} channel selective DCCAs. Isradipine is the most potent DCCA that is FDA approved for treatment of hypertension since 1990 (http://www.drugs.com/pro/isradipine.html). Isradipine is available in immediate release (IR) and was previously available in a controlled release (CR) preparation in 5-20 mg dose range. Peak serum levels occur in about 1.5 hours for the IR preparation and 8-10 hours for the CR preparation. The duration of the pharmacological effect of the IR preparation is 12 hours and 24 hours for the CR preparation after a single dose (for hypertension). Isradipine achieves maximal pharmacodynamic effect at a steady state in 2-4 weeks. Isradipine IR is administered twice daily. The serum concentration remains relatively stable for 24 hours once the steady state has been achieved. Isradipine is metabolized by CYP3A4 hepatic isoenzymes into at least 6 inactive compounds and excreted in

the urine (60-65%) and feces (25-30%). No initial dose adjustment for mild hepatic or renal impairment (creatinine clearance 30-80 ml/min) is required. Isradipine serum concentration can be affected by the compounds that block P-450 CYP 3A4 enzyme (see Section 5.2.11.1).

2.3 Isradipine Pharmacokinetic Data

There are limited published data on the pharmacokinetics of isradipine in normal volunteers [34, 35, 37-39]. There is no comparative PK data on isradipine CR vs. IR presented in the isradipine CR NDA application 020336 (Sandoz Pharm, data on file). Christensen et al (1993) has conducted a comparative study of pharmacokinetics and pharmacodynamics of Isradipine CR vs. regular in 30 subjects with moderate hypertension. The data are summarized in Table 1.

Table 1. Mean values and standard deviations (ranges for half-life) in brackets for the two dosages of isradipine (IR and CR formulations) after first dose and in steady state.

	C_{max} ng/ml	$T_{1/2}$ hr	AUC hr ng/ml	CI/F 1/hr
First dose				
2.5 mg x 1 (plain)	2.2 (0.9)	9.5 (3.6-24.5)	10.2* (4.4)	295 (148.5)
5.0 mg x 1 (SRO)	1.2	--	--	--
Steady state				
2.5 mg x 1 (plain)	2.3 (1.0)	13.1 (3.5 – 25.1)	9.9** (4.5)	314 (166.1)
5.0 mg x 1 (SRO)	1.8 (1.4)	-- --	23.1xx (11.6)	336.0 (321.9)

*: from 0 to infinity
**: from 0 to 12 hr
xx: from 0 to 24 hr

Based on the published PK data [40], we expect that in patients Isradipine IR 5 mg twice daily will achieve serum Cmax in the range of 5.53 ($\pm$2.80) ng/ml and Cmin in the range of 0.4 ($\pm$ 0.2) ng/ml[40].

We collected data on the trough plasma isradipine concentration across the 5-20mg daily dose exposure of Isradipine CR in PD subjects [unpublished data]. Blood samples for plasma isradipine concentration measurements were collected in the morning before the daily dose of the study drug (Cmin) at baseline and every 2 weeks during study visits. Plasma isradipine concentrations were measured by liquid chromatography-tandem mass spectrometry. Ten subjects participated in the PK substudy. Details of these findings are in Table 2. There was a good linear correlation between mean plasma isradipine concentration and isradipine dose in the 5-15 mg/day dose range. PK values were consistent with the data obtained from normal volunteers. The sample size for 20mg dose was not large enough to be reliable (n=4) as the majority of subjects in that sub-study cohort were

unable to tolerate a 20mg dosage.

Table 2. Mean plasma Cmin in PD subjects treated with escalating dosages of Isradipine CR

Isradipine CR Dose	5 mg	10 mg	15 mg	20 mg
N	10	9	9	4
Mean Plasma Cmin (± SD) (ng/mL)	0.68 ± 0.38	1.53 ± 0.72	2.53 ± 1.33	2.48 ± 1.16

Our data are consistent with the PK data provided by the manufacturer from the NDA application 020336 (Sandoz Pharm, data on file) for Isradipine CR in normal volunteers (Dynacirc CR) as seen in Table 3.

Table 3. Pharmacokinetics of Isradipine CR in normal volunteers

Study 162 Steady-state plasma isradipine modified release pharmacokinetic parameters Hours 0 – 24 on Day after once-daily dosing for 7-days each dosing period (n=27, except as indicated)			
	1 x 5mg	**2 x 5mg**	**4 x 5 mg**
	Mean, SD, min max	**Mean, SD, min, max**	**Mean, SD min, max**
AUC 0-24 h (ng*h/mL)	18.39,10.58 7.240, 54.67	35.00, 17.20 11.75, 87.41	65.30, 23.07 33.35, 117.56
Cmax (ng/mL)	**1.219, 0.689** 0.49, 3.50	**2.259, 1.104** 0.88, 5.08	**3.817, 1.315** 2.16, 6.75
Cmin (ng/mL)	**0.693, 0.455** 0.22, 2.34	**1.326, 0.613** 0.43, 2.71	**2.534, 1.087** 1.06, 5.61

In conclusion, there are sufficient data on the PK profile of Isradipine IR and CR in normal volunteers and hypertensive population to support comparable pharmacokinetics. Data generated from our studies of Isradipine CR in a PD population demonstrate comparable Cmin concentrations compared with studies in normal volunteers supporting the notion that there is no expected difference in PK profile of isradipine in a PD population versus a hypertensive population.

In addition, the above data support that isradipine 5 mg twice daily should provide serum concentration in the range of the level demonstrated to be neuroprotective in animal models.

2.4 Epidemiological Data

Recent epidemiological data also supports potential neuroprotective effect of DCCAs in PD: two studies demonstrated reduced risk of development of PD in subjects treated with calcium channel blockers (CCBs) compared to other antihypertensive agents[41], [42]. Ritz et al[42] assessed risk of the new diagnosis of PD in a cohort of 1,931 patients with new diagnosis of PD versus 9,651 matched controls [42]. The study demonstrated a 27% risk reduction (OR= 0.73) of a new diagnosis of PD in subjects treated with *centrally acting* DCCA *compounds* compared to other CCBs or other antihypertensive agents. That study provides strong supporting evidence of channel specific selectivity of potential neuroprotective effect of CCBs restricted to DCCA compounds. A more recent study by Pasternak et al[43] assessed risk of incident PD using the Danish Civil Registration system that contain information on all prescriptions filled by all of the country's pharmacies. The study concluded that use of DCCAs was associated with 29% (RR= 0.71) reduced risk of incident PD particularly in the elderly population (> age 65) as well as reduced mortality but not dementia.

In conclusion, there is solid scientific rationale, preclinical and epidemiological data to proceed with a clinical trial of isradipine, as a potential disease modifying agent in PD.

2.5 Isradipine Side Effect Profile

The side effect profile of isradipine is related to the primary mechanism of action of the agent as a vasodilator of the vascular smooth muscles and myocardium, and includes hypotension, bradycardia, weakness, and syncope. The most common adverse effect is peripheral edema as a result of the vasodilatory effect of the agent. The other known side effects include angina, asthenia, flushing, heart failure, palpitations, and dizziness. The only absolute contraindications for isradipine are hypersensitivity to dihydropyridine compounds and hypotension defined as systolic blood pressure below 90 mm Hg. **Table 4.** provides detailed safety and tolerability information on Isradipine IR as found in the package insert.

Table 4. The most common adverse events reported in US clinical trials for Isradipine IR

		Isradipine IR			Placebo	Active Controls*
Adverse Event	**All Doses**	**2.5 mg twice-daily**	**5 mg twice-daily†**	**10 mg twice-daily††**	**(N=297) %**	**(N=414) %**
Headache	13.7	12.6	10.7	22.0	14.1	9.4
Dizziness	7.3	8.0	5.3	3.4	4.4	8.2
Edema	7.2	3.5	8.7	8.5	3.0	2.9
Palpitations	4.0	1.0	4.7	5.1	1.4	1.5
Fatigue	3.9	2.5	2.0	8.5	0.3	6.3
Flushing	2.6	3.0	2.0	5.1	0.0	1.2
Chest pain	2.4	2.5	2.7	1.7	2.4	2.9
Nausea	1.8	1.0	2.7	5.1	1.7	3.1
Dyspnea	1.8	0.5	2.7	3.4	1.0	2.2
Abdominal discomfort	1.7	0.0	3.3	1.7	1.7	3.9
Tachycardia	1.5	1.0	1.3	3.4	0.3	0.5
Rash	1.5	1.5	2.0	1.7	0.3	0.7
Pollakiuria	1.5	2.0	1.3	3.4	0.0	<1.0
Weakness	1.2	0.0	0.7	0.0	0.0	1.2
Vomiting	1.1	1.0	1.3	0.0	0.3	0.2
Diarrhea	1.1	0.0	2.7	3.4	2.0	1.9

* Propranolol, prazosin, hydrochlorothiazide, enalapril, and captopril.
† Initial dose of 2.5 mg twice-daily followed by maintenance dose of 5.0 mg twice-daily.
†† Initial dose of 2.5 mg twice-daily followed by sequential titration to 5.0 mg twice-daily, 7.5 mg twice-daily, and maintenance dose of 10.0 mg twice-daily.
In open-label, long-term studies of up to 2 years in duration with immediate-release isradipine, the adverse events reported were generally the same as those reported in the short-term controlled trials. The overall frequencies of these adverse events were slightly higher in the long-term than in the controlled studies, but in the controlled studies most adverse reactions were mild and transient.

The safety profile of isradipine in the PD population has been explored in two studies.

2.6 Isradipine in PD Data

We have conducted an **Open label dose escalation safety and tolerability study of Isradipine CR in patients with early PD [44].** The study enrolled 31 subjects and demonstrated dose dependent tolerability of Isradipine CR: 94% for a 5 mg dosage; 87% for a 10 mg dosage; 68% for a 15 mg dosage; and 52% for a 20 mg dosage. Isradipine had no significant effect on blood pressure or PD motor disability. The two most common

reasons for dosage reduction were leg edema (7) and dizziness (3). There was no difference in isradipine tolerability between subjects with and without dopaminergic treatment. **Conclusion:** That study supports good tolerability of Isradipine CR at daily dosages up to 10 mg in subjects with early PD.

A pilot phase II double-blind, placebo-controlled, tolerability and dosage finding study of Isradipine CR as a disease modifying agent in patients with early Parkinson Disease (STEADY-PD) [36]. The objective of the study was to establish safety and tolerability of Isradipine CR across the FDA approved dosing range (5-20mg) in a larger cohort of patients with early PD and to evaluate comparative efficacy of three dosages of Isradipine CR provided that they are tolerable. The study recruited subjects with early PD not requiring dopaminergic therapy (stable dose of amantadine, anticholinergics and MAO-B inhibitors are allowed). The study was a multicenter 52 weeks, randomized, 4-arm double-blind parallel group trial with 100 subjects randomized to 5 mg, 10 or 20 mg of Isradipine CR or matching placebo daily. The dosage that was most tolerable and demonstrated preliminary efficacy was to be used in the proposed pivotal efficacy study. Tolerability of each active dosage was compared with the tolerability of placebo. Tolerability threshold was defined as more than 30% difference in the tolerability of each active treatment group relative to placebo. Provided that the dosage was tolerable, the choice for the dosage selection was to be based on efficacy defined as the change in total UPDRS score between the baseline visit and month 12 or the time of sufficient disability to require dopaminergic therapy (last visit before subject goes on dopaminergic therapy), whichever occurred first. *Comparison was made between three active treatment arms*. Power calculations for comparative efficacy analysis were made based on three point difference in total UPDRS between the active treatment groups. The dosage that demonstrated the greatest efficacy would be selected for the pivotal study. The study included a prespecified interim analysis for tolerability after 50 subjects had completed 12 weeks of the study.

Between September 2009 and October 2010, 115 subjects were screened and 99 enrolled in the study. There were 69 males, 30 females, predominantly White non-Hispanic, mean age at entry 59 (SD 9.77) years, average 0.95 (+ 0.92) years from diagnosis, with no imbalances among treatment groups. Mean total UPDRS (Part I-III) at entry was 25.02 (+9.9), with no significance imbalances. Compliance with the treatment was excellent (99.94% (SD 0.43) based on the pill count.

Tolerability of Isradipine CR. All subjects were included in the tolerability analysis based on the intention to treat. A pre-specified interim tolerability data analysis conducted by the DSMB in July 2010 (without breaking the blind of the investigators) showed that the Isradipine CR 20 mg dosage was intolerable. Based on the protocol, newly recruited subjects randomized to the 20 mg group after the results of the interim analysis became available were titrated to the 15 mg maximum dose (N=4). There were 8/99 early terminations, 5/8 occurred in the 20 mg dosage group with the others equally distributed between the groups. Dosage reductions and suspensions had a clear dose-response relation. In terms of the primary definition of tolerability, completing the study, there was no difference between the placebo, 5 mg and 10 mg groups. In terms of the secondary defi-

nition, completing without dosage adjustment (reduction or suspension due to intolerability) the numbers were 96% (25/26) for placebo, 83% (19/23) for 5 mg, 73% (19/26) for 10 mg, 50% (2/4) for 15 mg, and 35% (7/20) for 20 mg dose groups. Based on the above data, 5 and 10 mg dosages met pre-specified tolerability parameters. There was clear evidence of intolerability in the 20 mg group. The size of the 15 mg cohort (N=4) was small though also failed the tolerability parameters.

Safety: There were 7 (2 in placebo, 2 in 5mg, 1 in 10 mg, 2 in 20 mg arms) serious adverse events (SAE's), with scant evidence of any relationship to study drug. AEs affecting in aggregate over 5% of the subjects are presented in **Table 5**.

Table 5. Adverse events occurring in more than 5% of the PD participants:

Adverse Events		Placebo N(%)	5mg N(%)	10mg N(%)	15mg N(%)	20mg N(%)	Subjects
PERIPHERAL EDEMA	a.All	1(3.85)	4(17.39)	9(34.62)*	4(100.00)*	12(60.00)*	30
	b.wo/Mild	1(3.85)	0(0.00)	4(15.38)	1(25.00)	5(25.00)	
DIZZINESS	a.All	7(26.92)	5(21.74)	6(23.08)	1(25.00)	5(25.00)	24
	b.wo/Mild	2(7.69)	2(8.70)	0(0.00)	0(0.00)	0(0.00)	
NASOPHARYNGITIS	a.All	2(7.69)	4(17.39)	7(26.92)	0(0.00)	4(20.00)	17
	b.wo/Mild	2(7.69)	1(4.35)	1(3.85)	0(0.00)	0(0.00)	
HEADACHE	a.All	3(11.54)	3(13.04)	6(23.08)	0(0.00)	4(20.00)	16
	b.wo/Mild	1(3.85)	1(4.35)	1(3.85)	0(0.00)	0(0.00)	
CONSTIPATION	a.All	3(11.54)	2(8.70)	3(11.54)	0(0.00)	4(20.00)	12
	b.wo/Mild	0(0.00)	0(0.00)	2(7.69)	0(0.00)	1(5.00)	
FATIGUE	a.All	2(7.69)	1(4.35)	3(11.54)	0(0.00)	3(15.00)	9
	b.wo/Mild	1(3.85)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	
NAUSEA	a.All	3(11.54)	2(8.70)	1(3.85)	0(0.00)	2(10.00)	8
	b.wo/Mild	2(7.69)	1(4.35)	0(0.00)	0(0.00)	0(0.00)	
URT INFECTION	a.All	1(3.85)	2(8.70)	5(19.23)	0(0.00)	0(0.00)	8
	b.wo/Mild	0(0.00)	1(4.35)	0(0.00)	0(0.00)	0(0.00)	
DEPRESSION	a.All	2(7.69)	3(13.04)	1(3.85)	1(25.00)	1(5.00)	8
	b.wo/Mild	1(3.85)	1(4.35)	0(0.00)	0(0.00)	1(5.00)	
SOMNOLENCE	a.All	2(7.69)	3(13.04)	2(7.69)	0(0.00)	0(0.00)	7
	b.wo/Mild	0(0.00)	2(8.70)	0(0.00)	0(0.00)	0(0.00)	
INSOMNIA	a.All	2(7.69)	3(13.04)	1(3.85)	0(0.00)	0(0.00)	7
	b.wo/Mild	0(0.00)	2(8.70)	0(0.00)	0(0.00)	1(5.00)	
DYSPEPSIA	a.All	3(11.54)	1(4.35)	1(3.85)	0(0.00)	1(5.00)	6
DIARRHEA	a.All	2(7.69)	1(4.35)	2(7.69)	0(0.00)	1(5.00)	6
	b.wo/Mild	1(3.85)	0(0.00)	1(3.85)	0(0.00)	0(0.00)	
SINUSITIS	a.All	3(11.54)	2(8.70)	1(3.85)	0(0.00)	0(0.00)	6
	b.wo/Mild	2(7.69)	1(4.35)	0(0.00)	0(0.00)	0(0.00)	
BACK PAIN	a.All	1(3.85)	0(0.00)	2(7.69)	0(0.00)	3(15.00)	6

	b.wo/Mild	1(3.85)	0(0.00)	0(0.00)	0(0.00)	2(10.00)	
HYPOTENSION	a.All	1(3.85)	1(4.35)	2(7.69)	1(25.00)	1(5.00)	6
MUSCLE SPASMS	a.All	0(0.00)	2(8.70)	1(3.85)	0(0.00)	2(10.00)	5
	b.wo/Mild	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(5.00)	

*p< 0.05

Only peripheral edema showed imbalance between the four groups, with numbers 1,4,9,16 respectively. The trend persisted when events judged to be mild were eliminated (1,0,4,6). AEs that lead to dosage reduction or suspension included leg edema (N=14), dizziness (N=4), combination of two (N=2), and reduction of blood pressure (N=3).

There was no significant impact of the drug on blood pressure readings and no direct association of dizziness with the change in blood pressure and other vital signs. Six subjects (6%) reported hypotension as an adverse event and two had orthostatic hypotension (1 placebo, 1 in 20 mg dosage). One subject had rebound hypertension after drug withdrawal.

Efficacy: There was no statistically significant difference in the change in UPDRS or other variables between the active treatment groups. Adjusted differences in UPDRS between each active dosage group and placebo were 0.04 (SD 2.0) pts 5 mg, -1.10 (1.97) pts 10 mg, -2.00 (2.01) pts 20 mg. Positive signs denote worsening, negative signs improvement. *These results suggest a possible trend toward efficacy for the 10 and 20 mg dosage.* There was no evidence of any difference in the endpoint of disability requiring therapy among the four groups 15 (placebo), 14 (5 mg), 14 (10 mg), 11 (20/15 mg). All the Kaplan-Meier curves approximate a 50% endpoint rate at the one year.

There was no consistent evidence of a symptomatic effect of isradipine based on the wash-in or washout effects. Of note, the placebo group actually fared worst during the washout.

In conclusion, these studies demonstrate dose-dependent tolerability of Isradipine CR in patients with early PD and establishes 10 mg dosage as the tolerability threshold. Surprisingly, but consistent with the previously completed open label dosage escalation study Isradipine CR had no significant impact on blood pressure in our cohort. The safety profile of isradipine in the PD population was consistent with the isradipine package insert [45]. The most common AE was leg edema which is related to the potent vasodilatory effect of CCBs rather than fluid retention [46].

Based on the results of these studies, the 10mg dosage will be the target for the proposed pivotal Phase III study of isradipine as a potential disease modifying agent in early PD. That dose achieves serum concentration in the range that was neuroprotective in preclinical models of Parkinsonism.

3 STUDY DESIGN

3.1 Overview

The study is designed as a randomized Phase-3, 2-arm, double-blind, parallel group trial with subjects randomized to Isradipine IR 5 mg or matching placebo twice daily.

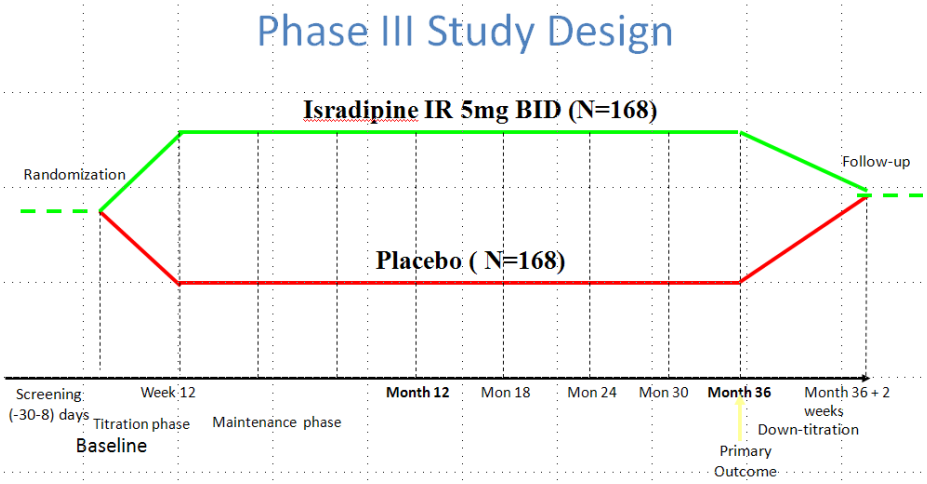
Primary efficacy analysis will be performed after all subjects complete 36 months on their randomized treatment assignment. We expect that nearly all subjects will require symptomatic therapy (e.g., levodopa or dopamine agonist) prior to the end of the 36 months study; if so they will still continue on their randomized treatment assignment in conjunction with the symptomatic therapy. In that case the primary statistical analysis will be based on UPDRS assessed in the medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy). Once a subject starts symptomatic therapy, the ON and OFF assessments should be completed for all PD medications including dopamine agonists, MAO inhibitors, or any other dopaminergic therapies.

3.2 Study Design Justification

PD is a slowly progressive neurodegenerative disease. A majority of the currently conducted studies designed to investigate the efficacy of the potential disease modifying agents enroll subjects with newly diagnosed PD not yet requiring symptomatic therapy and use the time to initiation of symptomatic therapy as either the primary outcome measure or the time to end point. While the limitations of such a design are well-recognized, it is driven by lack of objective biomarkers of PD progression and obvious impact of symptomatic therapy on standard clinical outcome measures. These factors justify at least initial testing of the putative disease modifying therapy in the cohort of de novo subjects. However, on average 50% of the subjects require symptomatic therapy in the course of 12 month studies [20].

The current study design (Fig. 2) will collect the primary outcome data on the efficacy of the intervention at 36 months with the objective to provide long term information on the efficacy, tolerability and safety of isradipine in PD. The collected data will inform us on the longer term benefit of Isradipine IR 5 mg twice daily mg on motor disability as measured by the change in the total UPDRS score between baseline and month 36. We expect that nearly all subjects will require symptomatic therapy (e.g. levodopa or dopamine agonist) prior to the end of the 36 months study; if so they will still continue on their randomized treatment assignment in conjunction with the symptomatic therapy and the primary outcome measure will be UPDRS measured in the medications ON state (see Section 8). We also will collect a number of secondary efficacy and safety outcomes even after the initiation of symptomatic therapy. This will allow us to explore if any short term effects of isradipine are maintained even after symptomatic therapy has been initiated.

Figure 2



4 SELECTION AND ENROLLMENT OF SUBJECTS

Approximately three hundred thirty-six (336) subjects with early idiopathic PD who do not require dopaminergic therapy will be enrolled. The inclusion and exclusion criteria are described below. The study is planned as a multi-center study with approximately 56 participating sites in North America. See Section 8 for justification of the sample size.

4.1 Inclusion Criteria

1. Subjects with early idiopathic PD (presence of at least two out of three cardinal manifestations of PD). If tremor is not present, subjects must have unilateral onset and persistent asymmetry of the symptoms
2. Age equal or greater than 30 years at the time of diagnosis of PD
3. Hoehn and Yahr stage less than or equal to 2
4. Diagnosis of PD less than 3 years
5. Currently NOT receiving dopaminergic therapy (levodopa, dopamine agonist or MAO-B inhibitors) and NOT projected to require PD symptomatic therapy for at least 3 months from the baseline visit
6. Use of amantadine and/or anticholinergics will be allowed provided that the dosage is stable for 8 weeks prior to the baseline visit
7. If subjects is taking any central nervous system acting medications (e.g. benzodiazepines, antidepressants, hypnotics) regimen must be on a stable for 30 days prior to the baseline visit
8. Women of childbearing potential may enroll but must use a reliable measure of contraception and have a negative serum pregnancy test at the screening visit

4.2 Exclusion Criteria

1. Subjects with a diagnosis of an atypical Parkinsonism
2. Subjects unwilling or unable to give informed consent
3. Exposure to dopaminergic PD therapy within 60 days prior to baseline visit or for consecutive 3 months or more at any point in the past

4. History of clinically significant orthostatic hypotension or presence of orthostatic hypotension at the screening or baseline visit defined as greater than or equal to 20 mmHg change in systolic BP ***and*** greater than or equal to 10 mmHg change in diastolic BP from sitting to standing after 2 minutes, or baseline sitting BP less than 90/60
5. History of congestive heart failure
6. Clinically significant bradycardia
7. Presence of 2nd or 3rd degree atrioventricular block or other significant ECG abnormalities that in the investigator's opinion would compromise participation in study
8. Clinically significant abnormalities in the Screening Visit laboratory studies or ECG
9. Presence of other known medical or psychiatric comorbidity that in the investigator's opinion would compromise participation in the study
10. Prior exposure to isradipine or other dihydropyridine calcium channel blockers (see list in Operations Manual) within 6 months of the baseline visit
11. Subjects on greater than 2 concomitant antihypertensive medications. If history of hypertension, then a maximum of 2 other antihypertensive agents will be allowed provided that the dosages of concomitant anti HTN therapy can be reduced/adjusted during the study based on the BP readings in consultation with the subject's primary care provider or cardiologist. Use of any concomitant calcium channel blockers will not be allowed from the baseline visit through the duration of the study
12. Use of grapefruit juice, ginkgo biloba, St. John's wort, or ginseng will be prohibited starting from the screening visit and for the duration of the study (as they interfere with the metabolism of isradipine)
13. Use of clarithromycin, telithromycin and erythromycin will be prohibited starting from the screening visit and for the duration of the study as the combination of clarithromycin, telithromycin or erythromycin and calcium channel blockers have been reported to be associated with increased risk of kidney and heart injury
14. Presence of cognitive dysfunction defined by a Montreal Cognitive assessment (MoCA) score of less than 26 at screening
15. Subjects with clinically significant depression as determined by a Beck Depression Inventory II (BDI) score greater than 15 at the screening visit
16. History of exposure to typical or atypical antipsychotics or other dopamine blocking agents within 6 months prior to the baseline visit
17. History of use of an investigational drug within 30 days prior to the screening visit
18. History of brain surgery for PD
19. Allergy/sensitivity to isradipine or its matching placebo or their formulations.
20. Pregnant or lactating woman

4.3 Study Enrollment, Recruitment and Retention Procedures

4.3.1 The study will be conducted at approximately 56 PSG clinical sites in North America. Each site employs a PSG-credentialed site Investigator and a Study Coordinator. Each site is required to have individual Institutional Review Board (IRB)/Research Ethics Board (REB) approval. All PSG site Investigators are well trained and qualified in the administration of the UPDRS and will be required to provide certification of training on the MDS-UPDRS. Training sessions will be performed at the orientation meeting with special emphasis on the primary outcome measure. New sites, identified after the orientation meeting, will be trained individually. Enrollment will be closed as soon as the 336 subjects have been enrolled. The clinical trial will be posted on a number of websites to include: NIH's clinical trials website, Clinicaltrials.gov, and the PSG website. Based on our prior experience with clinical trials in PD and the sites' feedback, we anticipate most subjects will be recruited for this trial through the site's center.

4.3.2 Once a study site has obtained IRB/REB approval, a site can start identifying potential participants for the study. Subjects that are asked to participate in this trial will be tracked on a Confidential Participant Log which is kept by the site study staff in a secure location. In addition information regarding how subjects learned about the trial, referral sources, reasons for ineligibility and reasons for non- participation for eligible subjects will be tracked on the Screening/Demographics form in the eClinical system for all subjects who have signed a consent and are screened for the study.

4.3.2.1 Subject Randomization /Enrollment

All subjects will be assigned a 4-digit Subject ID Number by the site that is provided by the Clinical Trials Coordinator Center (CTCC). Study drug will be precoded by the Clinical Materials Services Unit (CMSU) with Enrollment ID/randomization kit numbers (based on the randomization plan generated by the University of Rochester Biostatistics Department). Pre-assigned drug kits will be supplied to the site Investigator.

- The treatment for each subject will be assigned by a randomized code. A blocked randomization scheme will be used to ensure approximately even distribution of subjects in treatment groups at each site.
- Once the subject qualifies for the randomized phase of the study, the site Investigator or Study Coordinator will enter data into the eClinical system that will assign a unique Enrollment ID Number that will match a study drug kit. These numbers are assigned in a randomized order, rather than sequentially.
- The randomization algorithm and subject enrollment process will be implemented through the Internet accessible Electronic Data Capture (EDC) system using authenticated, password-protected accounts for each study site. The

EDC system will automatically validate inclusion/exclusion criteria and generate visit windows.

- Once the online enrollment process is completed, the site will print an Enrollment Verification Report that verifies the subject has been randomized. The report will note the Enrollment ID Number that was assigned that corresponds to the drug kit number and the upcoming study visit windows. If a site's EDC system is not operating, the site may alternatively call the CTCC for subject enrollment during designated working hours.
- Once a subject has been allocated an Enrollment ID Number this number cannot be assigned to another subject.

4.3.3 During or before a screening visit, the subject will be thoroughly informed about all aspects of the study, including all scheduled visits and activities, and will be able to ask questions. The subject will be requested to sign and date the informed consent form prior to undergoing any study-specific procedures. The original signed and dated informed consent form must be retained by the Investigator in the subject's file and a copy must be provided to the subject.

4.3.4 Identification Numbers

4.3.4.1 Subject Identification (ID) Numbers

Once a potential subject has signed informed consent, a Subject ID Number will be assigned in sequential order by the site from a list provided to the site by the CTCC. This 4-digit number will be used to identify the subject on all study forms and lab specimens.

4.3.4.2 Randomization/Enrollment Identification (ID) Number

An Enrollment ID Number will be assigned by the eClinical system at the randomization visit to confirm enrollment and proper receipt of the randomized study drug assignment. The Enrollment ID Number will be the same as the randomization/drug kit number on the study drug container.

4.3.4.3 CTCC Unique Identification (ID) Number

Subjects will be instructed how to obtain a 9-digit Unique Identification Number at the Screening Visit. This ID system has the ability to track individual subjects across multiple CTCC studies without storing any personally identifiable information. The protected system uses an algorithm of nine data element inputs (last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth, and mother's maiden name), and produces an electronic "fingerprint" output. The system stores only the "fingerprint" and clears the individual's inputted data elements from memory. The subject is then assigned a 9-digit CTCC

Unique ID Number that is associated with their electronic "fingerprint."

Once a subject signs the informed consent he/she will be directed to a secure website where he/she or the site Study Coordinator (if the subject requests/prefers) will enter the subject's nine data elements. The CTCC Unique ID Number will be printed and provided to the subject. The Study Coordinator will record this number on the Demographics Case Report Form (CRF).

If a subject has participated in previous CTCC studies and already has an existing CTCC Unique ID Number, this number will be used for this study. A subject can regenerate his/her CTCC Unique ID Number. He/She can return to the secure website, enter the same nine data elements in the exact same way they were entered the first time and will receive their same CTCC Unique ID Number.

4.4 Strategies for Retention

Multiple retention initiatives will be rolled-out to sites intermittently throughout the study to enhance subject retention and to provide various avenues for communication with sites and subjects. Since study visits occur at 6-month intervals after Month 12 (Visit 06), retention strategies will be key to minimizing subject withdrawals. Visit reminders and incentives for visit attendance and protocol adherence may include pocket/wallet reminder cards, birthday cards, holiday cards, backpacks, lunch boxes, luggage tags, refrigerator reminder magnets and subject newsletters.

In addition, a third-party moderator facilitated webinar between study subjects and study investigators, is planned, which will provide study updates and emphasize the importance of subject retention. All meeting materials will be IRB approved prior to implementation. Study subjects will be able to ask questions of investigators through a moderator in order to minimize providing information to study subjects that could compromise the scientific integrity of the study.

5 STUDY INTERVENTIONS

5.1 Study Drug Administration and Duration

The study will use Isradipine IR 2.5 mg oral capsules and matching placebo. Subjects will administer either isradipine or placebo capsules twice daily for 36 months.

5.2. Study Drug Management

5.2.1 Packaging

Study drug [Isradipine IR 2.5mg] will be purchased from the manufacturer. To maintain the blind, study drug will be over encapsulated and Placebo to Match (PTM) capsules will be manufactured and packaged into its primary container closure system. A total of 130 capsules of 2.5 mg active Isradipine IR or PTM (0mg Isradipine) will be packaged in each bottle. **Each bottle will provide 32 days (1 month) supply of the study drug that will be administered as 2X 2.5 mg capsules twice daily.**

The Clinical Materials Services Unit (CMSU) in the Center of Human Experimental Therapeutics (CHET) at the University of Rochester will provide secondary packaging, labeling and distribution services. CMSU will create identically matching 6 month kit boxes containing six (6) 130 capsule count bottles per kit box. Each subject is expected to receive six (6), six (6) month kits for this 3 year study.

In order to prepare subject study drug kits, CMSU will receive the randomization codes and attendant study drug assignment from the Biostatistician at the University of Rochester.

5.2.2 Labeling

At a minimum the following information will be included on each six (6) month kit box and each bottle:

- Name and address of distribution center
- Study number/Acronym
- Name of the product
- Pharmaceutical dosage form
- Route of administration
- Quantity of dosage unit
- Directions for use
- Storage conditions
- Space for information to be completed by Investigator/designee:
  - Name and telephone number of Investigator
  - Dispensing Date
  - Subject Number
- Statement "Caution: New Drug – Limited by law to investigational (clinical trial) use"
- Statement: "Keep out of reach of children"

Labeling will be in both English and French-Canadian text.

5.2.3 Storage

All drug supplies should be stored at controlled room temperature, 20°-35°C (68°-77°F). The study drug must also be stored in a secure location with limited access.

5.2.4 Accountability of Study Drug Supplies

Study drug will be shipped from CMSU to each participating site. Sites will be required to acknowledge receipt of study drug within 48 hours of receiving a shipment. The site Investigator, Study Coordinator, or Pharmacist must maintain accurate records (including dates) of all supplies received. All study drug supplies issued to, used by, and returned by each subject must be recorded on a Drug Dispensing/Return Log completed by the Investigator, Study Coordinator, or Pharmacist. Subjects will return all unused study drug, including empty bottles to the site Investigator. After reconciliation, and CTCC written approval, all remaining study supplies (opened and unopened) including empty bottles may be destroyed at the investigational site per site institutional policy.

5.2.5 Coding/Emergency Drug Disclosure

The Investigator or site Pharmacist (if applicable) will be given a sealed envelope containing a set of individual sealed envelopes, each containing the drug code for each subject. All sealed code envelopes will be returned to the University of Rochester Biostatistics Center at the conclusion of the study, where they will be inspected to ensure that they have not been opened. An individual subject's envelope or label should be opened only in the case of a medical emergency. If such action is required, the CTCC Clinical Monitor must be notified first, if circumstances permit, rather than disclosing the randomization. If a drug disclosure is made, a record must be made by the Investigator/Pharmacist detailing the purpose, date and personnel involved.

Neither premature withdrawal from the study nor most clinical emergencies necessitate disclosure of treatment assignment. Most emergency situations can be handled by withdrawing study drug without disclosure of treatment assignment. However, in rare circumstances under which knowledge of the drug assignment is necessary for the treatment of an adverse event, site Investigators must make every attempt to discuss the situation with the CTCC Clinical Monitor before deciding whether or not to disclose treatment assignment. If disclosure of individual treatment assignment is undertaken it must be made by the Investigator responsible for the care of the involved subject (or by the Coordinator or other physician as designated by the Investigator). The subject will be withdrawn from further exposure to study drug. In accordance with the intent-to-treat principle these subjects will be encouraged to remain in the study and every attempt will be made to continue to follow them and obtain the primary outcome data.

The disclosure envelope/label and contents should be sent to the University of Rochester Biostatistics Center within 48 hours of the disclosure. Assigned drug treatment must not be revealed to other study staff, CTCC staff or to individuals who are not involved directly in the clinical care of the subject unless disclosure to him/her is critical to the care of the subject. See Section 4 of the Operations Manual for additional information and instructions.

5.2.6 Dosage of Study Drug

Subjects will initiate study drug at a dosage of 2.5 mg twice daily or matching placebo (1 capsule twice daily) and titrate to 5 mg twice daily or matching placebo (2 capsules twice daily) after the first 2 weeks. Study drug must be taken twice daily approximately 12 hours apart with or without food. Subjects must remain on 5 mg daily dosage level a minimum of 14 days prior to upward titration to 10 mg daily dosage (2 capsules twice daily). Titration period may be extended if a dosage escalation is delayed due to a need to reduce a concomitant antihypertensive agent as a result of orthostatic hypotension (see *Rules for Study Drug Titration* below).

In addition, random dose adjustments may be done in both study groups (active or placebo) using an algorithm devised by the Biostatistician at the University of Rochester in order to preserve the study blinding. All subjects have to enter the maintenance phase no later than at Visit 03 (Month 3). Dosage reductions will be allowed for intolerability (see Section 5.4).

5.2.7 Study Drug Titration

Blood Pressure Monitoring:

1. All subjects will require home blood pressure monitoring for at least 7 days prior to baseline. Blood pressure monitoring continues during dose titration.
2. Using a home digital blood pressure device, subjects will obtain blood pressure readings at home twice daily in the morning and in the evening, approximately 12 hours apart. The blood pressure readings will be obtained in a sitting position and after 2 minutes in a standing position. Blood pressure recordings will be uploaded via internet access in real time to the BP Vendor. During drug escalation or de-escalation, site investigators and study staff will be blinded to home blood pressure recordings unless unblinding is warranted for subject safety. Home blood pressure recordings will be monitored remotely by an assigned BP Clinical Monitor who will have acess to the BP vendor web-based database. The BP Clinical Monitor will communicate with the Site Investigator if needed to discuss drug titration management.
3. During drug titration, the BP Clinical Monitor will have access to the BP Vendor database and will assess home blood pressures out of range to include Systolic Blood Pressure less than 90 mmHg or greater than 160 mmHg and Diastolic Blood Pressure less than 60mmHg or greater than 90 mmHg.
4. Site Investigators and Coordinators will have limited access to the BP vendor web-based blood pressure database, in order to maintain the blind, and will be required to access the database prior to the Baseline visit and for each visit during drug titration to confirm titration can continue. The database will provide site staff with a confirmation notice to state that titration can proceed or cannot proceed. The Site Investigator and Coordinator will not be able to view BP data on the vendor website. See Section 13 of the operations manual for additional information on the site staff access to the website. Random delays

in dose titration may be done in both study groups (active or placebo) at the direction of the Biostatistician at the University of Rochester in order to preserve the study blinding.

5. For subjects where the BP vendor confirmation message states drug titration may proceed, confirmation of in-person blood pressure readings must also meet titration requirements as outlined in "*Rules for Study Drug Titration*" below.
6. For subjects where titration cannot proceed, the Site Investigator may contact the Clinical Monitor to obtain information on additional BP data, if needed. The CTCC Project Manager should be notified within 24 hours of any reduction or suspension of drug titration. See Section 7 of the Operations Manual for guidance on reporting requirements.

Rules for Study Drug Titration:

1. The ***average*** home blood pressure readings and in-person blood pressure (BP) readings must meet pre-specified criteria (see Section 4 and Section 13 of Operations Manual) and the subjects should not have orthostatic BP changes to proceed with randomization. **Orthostatic changes are defined as: greater than 20 mmHg drop in systolic BP AND greater than or equal to 10 mmHg drop in diastolic BP from sitting to after 2 minutes of standing.** Site staff may repeat blood pressure readings after 20 minutes if the initial in-person blood pressure does not meet the required criteria.
2. Dosage escalation can only take place at or after an in-person visit (either regularly scheduled or unscheduled depending on the timing of the dosage escalation) provided the Investigator receives a confirmation notice to proceed from the BP vendor website and the in-person BP readings meet the pre-specified criteria.
3. During the titration period the subject must escalate no sooner than every 14 days (see titration instructions below). If the subject is seen prior to 14 days (out of the window at V01 or 14 days after last titration) the subject must complete a full 14 days of treatment before going to the next dosage level.
4. Dosage reductions can occur for intolerance to study drug for *any reason at any time* during the study (see Section 5.4).
5. Resuming dose titration (re-challenges) will be allowed at any time during the study at the discretion of the Investigator. In general, the Investigator should limit re-challenges to no more than two attempts per subject unless the Investigator has a specific reason for doing so (change in subjects concomitant antihypertensive, new AE being addressed etc.).
6. For the subjects **treated with antihypertensive agents** whose ***average*** BP does not meet the pre-specified criteria (see Section 4 of the Operations Manual) the dosage of concomitant antihypertensive agent can be reduced after consultation with the primary care provider (PCP) or cardiologist. This consultation must be clearly documented in the source documents. Further reduction of the dosage of antihypertensive agent will be allowed if necessary. The dosage of the study drug should not be increased for <u>at least a week</u> after ad-

justment of the concomitant antihypertensive dose and only after the Investigator receives a confirmation notice to proceed from the BP vendor website and the in-person BP readings meet the pre-specified criteria.. Further study drug dosage escalation should follow the standard titration schedule as discussed below in section 5.2.7, with increases no sooner than every 14 days.

7. During the maintenance phase, the dosage of concomitant antihypertensive agent can be reduced at any point in the study after consultation with the primary care provider or cardiologist. This consultation must be clearly documented in the source documents. For hypotensive symptoms, the dosage of the concomitant antihypertensive agent should be reduced prior to considering a reduction of the dosage of the study drug.
8. **The study drug must ALWAYS be taken twice daily unless a subject requires dosage reduction to 2.5 mg *once* daily due to intolerability (see Section 5.4).**
9. If dosing has not occurred for 4 hours or more from scheduled dosing time, the missed dose should be skipped.

5.3. Study Visit Instructions

The Visit Status case report form is required for each study visit and telephone contact whether or not the visit or call was actually performed. This form documents whether or not the visit took place and the reasons why if it didn't. It also serves as a reminder to update the AE Log, Concomitant Medication Log, Dose Management Log, and the Drug Dispense and Return Log, if needed.

Baseline Visit (Day 0) Instructions:
Drug randomization will occur at the Baseline visit after review of all inclusion/exclusion criteria, receipt of confirmation from the BP vendor website to proceed and the in-person BP readings meet criteria for dosage escalation and review of vital signs obtained at the site visit. After entering data into the eClinical system, the site will be given a Randomization/Enrollment ID number that will correspond to a drug kit. Record this number on the drug dispensing/return log. Dispense only Bottle 1 from the kit that has been assigned during the randomization process. The subject who meets BP criteria at the Baseline visit should be instructed to take **one capsule from Bottle 1**, twice daily (with or without food) in the morning after recording their morning blood pressure, and in the evening (approximately 12 hours after the morning dose) after recording their evening blood pressure. The subject should continue to take the study drug, unless intolerable side effects develop, until they are seen for Visit 01. Advise the subject to report any side effects and changes in medication immediately to study staff.

In case of intolerability, the dosage of study drug should be reduced until intolerability resolves or the subject is off the study drug (see Section 4 of Ops Manual). Subjects who are unable to tolerate even the lowest dosage of study drug should be encouraged to remain in the study off the study drug.

For intolerability, dosage reduction should be attempted prior to discontinuing study drug (see Section 5.4). Instructions for dosage reduction can be given either over the phone after review of the adverse events or at the corresponding in-person visit (either regularly scheduled or unscheduled visit depending on the timing of the dosage reduction). For individuals on concomitant anti-hypertensive medication with adverse events referable to hypotension, reduction in the anti-hypertensive agent should be undertaken first (see Section 5.2.7 #7 above). Resumption of titration should happen at least a week later only at or after the in-person visit (either regularly scheduled or unscheduled visit depending on the timing of the dosage escalation) and after the Investigator receives the confirmation notice to proceed from the BP vendor website and the in-person BP readings meet criteria for dosage escalation. Subjects may resume titration to 5 mg twice daily dosage (2 capsules twice daily) at the discretion of the site Investigator provided blood pressure parameters are stable and the other intolerability issues have resolved (see Section 5.5 for re-challenge directions).

Visit 01 (Day 14/ + 3 days) Instructions:
After the Investigator receives the confirmation notice from the BP vendor website to proceed and the in-person BP readings meet criteria for dosage escalation., the subject should be instructed to begin taking **two capsules twice daily from Bottle 1 no sooner than day 15.** Study drug is taken twice daily (with or without food) in the morning after recording their morning blood pressure and in the evening (approximately 12 hours after the morning dose) after recording their evening blood pressure. The subject should continue to take the study drug, unless intolerable side effects develop, until they are seen for Visit 02. Advise the subject to report any side effects or changes in medication immediately to study staff. In case of intolerability, dosage reduction should be attempted prior to discontinuing study drug (see Section 5.4 for dose reduction instruction). For individuals on concomitant anti-hypertensive medication with adverse events referable to hypotension, reduction in the anti-hypertensive agent should be undertaken first (see 5.2.7 #7 above).

Visit 02 (Day 28 /+ 3 days) Instructions:
After the Investigator receives the confirmation notice from the BP vendor website to proceed and the in-person BP readings meet criteria for dosage escalation., the subject should be instructed to continue taking **two capsules twice daily (unless a dosage reduction has taken place)**. Subjects will be provided with 6 months study drug kits containing the remaining 5 one-month supply bottles. Study drug is taken **2 capsules twice daily** (with or without food) in the morning and in the evening, approximately 12 hours after their morning dose. The subject should continue to take the study drug, unless side effects develop, until they are seen for Visit 03. Subjects should be instructed to use all of the capsules in one bottle before opening the next bottle of study drug. Advise the subject to report any side effects or changes in medication immediately to study staff. In case of intolerability, dosage reductions should be attempted prior to discontinuing study drug. For individuals on concomitant anti-hypertensive medication with adverse events referable to hypotension, reduction in the anti-hypertensive agent should be undertaken first (see Section 5.2.7 #7). Instructions for dosage reduction and re-challenges are per the Section 5.3.

5. 4 Study Drug Reductions

Dosage reductions can occur at any time during the study. Random dose adjustments may be done in both study groups (active or placebo) at the direction of the Biostatistician at the University of Rochester in order to preserve the study blinding. In case of intolerability, dosage reduction should be attempted prior to discontinuing study drug. Instructions for dosage reduction may be given either over the phone after review of the adverse events or at the corresponding in-person visit (either regularly scheduled or unscheduled visit depending on the timing of the dosage reduction). See below for dosage reduction directions. **For individuals on concomitant anti-hypertensive medication with adverse events referable to hypotension, reduction in the anti-hypertensive agent should be undertaken first** (see 5.2.7 #7 above).

Subjects will reduce their dosage in a blinded fashion by 1 capsule (equivalent to 2.5 mg of Isradipine IR or placebo) each week. Dosage reduction should start by withdrawing a capsule from AM dose if on 10mg daily dosing (2 capsules twice daily). Subjects unable to tolerate 7.5mg dosage (one capsule in AM and two capsules in the evening daily) after a week will be instructed to reduce the dosage further to one capsule twice daily (equivalent to 5 mg Isradipine IR or placebo daily). Subjects unable to tolerate 5 mg daily dosage after a week will be instructed to reduce the dosage further to one capsule once daily taken in PM (equivalent to 2.5 mg Isradipine IR or placebo daily). Subjects unable to tolerate 2.5 mg daily dose will be taken off the study drug. In accordance with the intent-to-treat principle these subjects will be encouraged to remain in the study and every attempt will be made to continue to follow them and obtain the primary outcome data.

All study drug reductions must be called to the CTCC.

5.5 Study Drug Re-challenge (Resumption of Titration)

Titration should be completed by Visit 03, Month 3. Visit 03 will be the formal beginning of the maintenance phase of the study.

Resumption of titration can occur through the titration period at the discretion of the Investigator. Re-challenges following dosage reductions may occur at any time during the study (titration or maintenance).

Subjects may resume titration to 5 mg twice daily dosage (2 capsules twice daily) at the discretion of the site Investigator provided the in-person BP readings meet criteria for dosage escalation and other tolerability issues have resolved. The dosage should be increased by one capsule twice daily (as per initial titration every two weeks) until the subject is on 2 capsules twice daily or intolerability recurs. At the discretion of the Investigator titration can be done in increments of 2.5 mg (1 capsule) always adding the evening dose first. Subjects that are unable to tolerate a dosage increase will be reduced to the highest tolerated dosage [either 7.5 mg (2.5 mg in the AM and 5 mg in the evening, 5 mg

(2.5 mg twice daily) or 2.5 mg daily (one capsule in the PM) dosage] and enter the maintenance phase of the study. Subjects unable to tolerate 2.5 mg daily (one capsule in the PM) dosage will be taken off the study drug and will be encouraged to remain in the study.

All attempts at re-titration of study drug must be called to the CTCC.

5.6 Study Drug Suspension

Study drug may be temporarily suspended by the site Investigator. Drug suspensions lasting more than 3 days requires re-titration. If drug suspension is less than 3 days, the subject can restart drug at prior dosing level. This must be carefully documented on the Dose Management Log.

For drug suspensions lasting more than 3 days, subjects may be re-titrated starting at one capsule twice daily (2.5 mg or matching placebo) and increasing to 2 capsules twice daily in 14 days.

Home blood pressure monitoring is not required for re-titration and is only required at the beginning of the study during the initial titration.

All study drug suspensions must be called to the CTCC.

5.6.1 Study Drug Taper at Visit 10 (Month 36) or for Premature Withdrawal

Study drug taper will be started the day after Visit 10 or at Premature Withdrawal. Subjects will taper their dosage to 5 mg of Isradipine IR or placebo (equivalent to dose reduction to one capsule twice daily) every 2 days. If a subject has already decreased their dosage due to prior intolerability to 5mg or 2.5 mg daily, then they will discontinue the drug at the start of the taper. The subject should be instructed to take the study drug (with or without food) in the morning) and in the evening. .

Written directions for drug tapering should be given to the subject. Advise the subject to report any side effects or changes in medication immediately to study staff.

5.6.2 Warnings/Precautions

- The side effect profile of Isradipine IR is related to the primary mechanism of action of the agent as a vasodilator of the vascular smooth muscles and myocardium, and includes hypotension, bradycardia, weakness, and syncope. The most common adverse effect is peripheral edema as reflection of the vasodilatory effect of the agent. The other known side effects include angina, asthenia, flushing, heart failure, palpitations, and dizziness. According to the package insert, the adverse effects are usually not serious, are dose dependent, and respond well to dosage reduction or discontinuation of therapy. Isradipine IR has no effect on atrioventricular or sinoatrial conduction. A full list of potential Is-

radipine IR related adverse events is available at: http://www.drugs.com/pro/isradipine.html. The safety profile of Isradipine IR in the PD population has not been systematically studied (see Section 2.5 for information on the side effect profile).

- Isradipine serum concentration can be increased by the compounds that block P-450 CYP 3A4 enzyme. Examples of inhibitors of CYP 3A4 include conivaptan, amiodarone, anti-retroviral protease inhibitors, systemic anti-fungals, and other agents (see list in Operations Manual). Use of these compounds is allowed but the subjects should be monitored for potential adverse events related to increase in the drug serum concentration. ***Grapefruit juice, ginkgo biloba, ginseng*** **are CYP3A4 inhibitors and are prohibited in this study.**
- Use of clarithromycin, telithromycin and erythromycin will be prohibited starting from the screening visit and for the duration of the study as concomitant use of clarithromycin, telithromycin or erythromycin with calcium channel blockers has been reported to be associated with increased risk of kidney and heart injury.
- Isradipine serum concentration can be reduced by the compounds that induce P-450 CYP 3A4 enzyme (see list in Operations Manual). ***St. John's wort*** **is CYP 3A4 inducer and will be prohibited in this study.**
- Calcium channel blockers including isradipine should be used cautiously in patients with gastroesophageal reflux (GERD) or hiatal hernia as these agents relax esophageal sphincter.
- Female subjects of childbearing potential will be advised to use adequate birth control throughout the study as the effects of Isradipine IR on the fetus are unknown. Adequate birth control methods include surgical sterilization, a partner who has had a vasectomy, oral contraceptives, condom plus spermicidal cream/jelly, cervical cap plus spermicidal cream/jelly, diaphragm plus spermicidal cream/jelly, or intrauterine device (in place for at least 3 months) plus spermicidal cream/jelly. Abstinence is considered an acceptable contraceptive regimen. Birth control should continue for two weeks after study drug has been discontinued.

  If a subject becomes pregnant during the study, it is important that they contact the site Investigator immediately. If a subject reports a pregnancy, study drug must be tapered immediately. ***Any subject becoming pregnant during the study will be tapered from the study drug immediately and can continue to participate in the study off of study drug. In addition, all attempts will be made to follow the subject until delivery. The pregnancy must be reported immediately to the CTCC.***
- The only absolute contraindications for Isradipine IR are hypersensitivity to dihydropyridine compounds and hypotension defined as systolic blood pressure below 90 mm Hg.

- Isradipine IR should be used with caution in subjects with bradycardia. Subjects with clinically significant bradycardia (as determined by Investigator) will be excluded from the study.

- Calcium channel blockers, including isradipine, have been shown to have negative inotropic effect on cardiac functions and may therefore exacerbate heart failure in patients with reduced left ventricular systolic function, regardless of current symptoms.

  Per the Physician's Desk Reference 2012 Warnings/Precautions: "Although acute hemo-dynamic studies in patients with congestive heart failure have shown that immediate-release DynaCirc® (isradipine) reduced afterload without impairing myocardial contractility, it has negative inotropic effect at high doses *in vitro* and possibly in some patients. **Caution should be exercised when using Isradipine IR in congestive heart failure patients, particularly in combination with a beta-blocker**."

  Investigators are encouraged to exercise caution when enrolling subjects with a history of myocardial infarction with a subsequent reduced ejection fraction or those with a documented reduction (less than 40%) in their ejection fraction or concomitant beta-blockers.

5. 7 Concomitant Medications

5.7.1 Allowed Concomitant Medications

Subjects with history of hypertension treated with no more than 2 other antihypertensive agents except for calcium channel blocking antihypertensive agents (see list in Section 2 of the Operations Manual) will be allowed provided that the dosages of concomitant anti hypertensive therapy can be reduced/adjusted during the study based on the BP readings in consultation with the subjects primary care provider or cardiologist. Procedures for the adjustment of the concomitant antihypertensive therapy are outlined in section 5.2.

Use of amantadine, or anticholinergics will be allowed. The dosage has to be stable for 8 weeks prior to baseline visit and for the duration of the study if feasible. Initiation or an increase in dosage of these medications or the initiation of dopaminergic therapy during the study will result in the subject reaching time for symptomatic treatment and all assessments as described in the symptomatic treatment visit will need to be completed. Any change in the dosage of these medications will require CTCC notification.

A stable regimen of central nervous system acting medications (benzodiazepines, antidepressants, hypnotics) is allowed. The dosage has to be stable for 30 days prior to the baseline visit. The dosage can be adjusted during the study at the discretion of the Investigator. Central nervous system acting medications can be initiated during the study, if needed, at the discretion of the Investigator.

5.7.2 Disallowed Medications

The following medications are not allowed during subject participation in the study:

- Use of calcium channel blockers (see list in Section 2 of the Operations Manual).
- Use of antipsychotics or other dopamine blocking agents within 6 months of the baseline visit and for the duration of the study. Only the atypical neuroleptics, clozapine and quetiapine, will be allowed during the study at the discretion of the Investigator.
- Use of grapefruit juice, ginkgo biloba, St. John's wort or ginseng (as they interfere with the metabolism of isradipine) starting from the screening visit and for the duration of the study.
- Use of clarithromycin, telithromycin and erythromycin will be prohibited starting from the screening visit and for the duration of the study as concomitant use of clarithromycin, telithromycin or erythromycin and calcium channel blockers has been reported to be associated with increased risk of kidney and heart injury. If antibiotic treatment is required, use of antibiotics other than clarithromycin, telithromycin or erythromycin is recommended. If clarithromycin, telithromycin or erythromycin treatment is required, study drug should be stopped through the duration of treatment and restarted after treatment per the re-titration rules above (see Section 5.3).
  Fentanyl anesthesia use has been associated with hypotension with concomitant use of calcium channel blockers and should be avoided if possible.
  If any disallowed medications are required and cannot be discontinued, study drug should be stopped and the subject should continue to be followed in the study off of study drug. Once a disallowed medication is stopped, the subject should be restarted on study treatment per the re-titration rules above (see Section 5.3).

5. 8 Adherence Assessment

AT EACH STUDY VISIT, THE SITE INVESTIGATOR AND/OR STUDY COORDINATOR WILL ASSESS THE SUBJECT'S ADHERENCE WITH THE STUDY REQUIREMENTS. THIS WILL INCLUDE CHECKS OF PROTOCOL COMPLIANCE, CONCOMITANT MEDICATION USE, BLOOD PRESSURE RECORDS, AND USE OF STUDY DRUG IN ORDER TO ASSESS THE RELIABILITY OF SUBJECT-GENERATED DATA. USE OF STUDY DRUG (PILL COUNTS) WILL BE ASSESSED AT VISIT 01 AND EVERY SCHEDULED DRUG RETURN VISIT THEREAFTER. IN EXTREME CIRCUMSTANCES SUBJECTS WHO CONSISTENTLY FAIL TO COMPLY WITH THE STUDY REQUIREMENTS MAY BE WITHDRAWN FROM THE STUDY. 6 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Activities (see page 17)

6.2 Timing of Evaluations

6.2.1 Screening Visit (Visit SC)

The Screening Visit will take place within 8 to 30 days of the Baseline Visit.

Prior to performing any study activity, the subject will be thoroughly informed on all aspects of the study, including all scheduled visits, activities, and procedures, and will be requested to sign and date the IRB/REB approved informed consent form. Subjects who have signed an informed consent form will be assigned a subject ID number. A 9-digit CTCC Unique Identification Number will also be assigned if the subject consents for the use of 9 pieces of information required to obtain the CTCC Unique Identification Number for use in future research

The Investigator will assess subjects for study eligibility. All the inclusion criteria must be met and none of the exclusion criteria may apply unless the site is given a waiver (exception) by the study PI or designee for particular criteria. See Section 3 of the Operations Manual for additional information and instructions on the requirements for waivers. All results from the Screening Visit procedures must be available before determining a subject's eligibility for the study.

Procedures & Evaluations

- Obtain written informed consent
- Request the name of the subject's primary care provider and cardiologist, if applicable
- Subject ID Number assigned
- Obtain a 9-digit CTCC Unique Identification Number, if subject agreed to in Informed Consent form
- Inclusion/Exclusion criteria
- Demographics
- Document PD diagnosis date and PD Features
- Assess primary diagnosis/probability of PD
- Assess socio-economic status
- Assess family history of PD
- Medical and Neuro History (General)
- General Neurological Exam
- General Physical Exam
- Concomitant Medication Log
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Beck Depression Inventory-II (BDI-II)
- Montreal Cognitive Assessment Scale (MoCA)

- Vital Signs (blood pressure, heart rate, temperature, weight, height)
- Safety Laboratory tests (serum chemistry, hematology, urinalysis)
- Collect blood sample for DNA and Biomarker, if subject agreed in consent form
- PK plasma sample
- Plasma sample for storage for future potential biomarker studies (only for subjects who consent for biomarker sampling)
- Serum pregnancy test – Complete for all women unless they are one year postmenopausal or surgically sterile
- Electrocardiogram (12-lead ECG)
- Assess Need for Symptomatic Therapy
- Modified Hoehn & Yahr Scale
- Training on Home Blood Pressure Monitoring

Instruct subjects: Subjects should be instructed how to use the home digital blood pressure monitoring device. Subjects' proficiency on using the device should be tested in the office by confirmation they are able to follow the written instructions provided. Subjects should be instructed to obtain blood pressures twice daily, in the morning and at bedtime, approximately 12 hours apart. A minimum of 7 complete days of blood pressure data must be available for the generation of a may proceed confirmation from the BP vendor website at the Baseline visit.

Subjects should be instructed to immediately report any adverse events or changes in concomitant medications to the site Investigator or Coordinator.

Record all above activities in source documentation, including the process of obtaining the informed consent.

6.2.2. Baseline Visit (Visit BL, Day 0)

The Baseline Visit must be within 8 to 30 days of the Screening Visit. All laboratory results, including blood work and ECG must be reviewed prior to the Baseline visit. A minimum of 7 complete days of blood pressure data must be available for the generation of a proceed confirmation from the BP vendor website.

Subjects will be randomized to one of the two treatment groups according to a computer-generated randomization scheme and will be assigned an Enrollment ID number. Subjects will be provided with study drug labeled with the same Enrollment ID number.

Procedures & Evaluations

- Review Inclusion/Exclusion criteria to ensure subject is eligible
- Review laboratory results from Screening Visit
- Review ECG

- Concomitant Medication Log
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Vital Signs (blood pressure, heart rate, temperature, weight)
- Generate a proceed or not proceed confirmation from BP vendor website
- Modified Rankin Scale
- PD Quality of Life Scale (PDQ-39)
- Quality of Life in Neurological Diseases (Neuro-QOL)
- Unified Parkinson's Disease Rating Scale (UPDRS) – Parts I, II, III *the motor portion of the UPDRS must be completed by the Investigator at each visit.*
- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Assess Need for Symptomatic Therapy
- Modified Hoehn & Yahr Scale
- Modified Schwab & England Activities of Daily Living
- Mini Environmental Risk Questionnaire (MERQ)
- Exercise Questionnaire
- Randomization/Enrollment ID Number assignment once all eligibility criteria are met
- Study Drug Dispensing – begin titration of study drug (see Section 5.2.7)
- Drug Dispensing/Return Log
- Dose Management Log
- Adverse Event Log – see Section 9.4.
- Instructions on blood pressure recording

Administration of study drug: The first dose of study drug is to be taken the next day in the morning (see Section 5.2, Study Drug)

Compliance and study drug storage requirements: subjects to bring study drug bottles at each visit (whether or not empty), and store study drug at proper temperature.

Instruct subjects: Subjects should be instructed to take their blood pressure twice daily, in the morning and in the evening, approximately 12 hours apart, BEFORE taking study drug.

Subjects should be instructed to immediately report any adverse events or changes in medication to the site Investigator or Coordinator.

Record all above activities in source documentation.

6.2.3 Visit 01 (Day 14 +3 days) and Visit 02 (Day 28 + 3 days)

During the titration period, Visits 01-02, visits can occur within a three-day window (+ 3). Whenever possible, subjects should not be seen prior to the target date.

For subjects who require reduction of antihypertensive medication, an additional *Unscheduled visit* may be scheduled to complete the titration. This visit should be scheduled at least 7 days following the reduction of the concomitant antihypertensive agent (see Section 5.2.7 for instructions on dose titration) and should include all procedures performed at Visit 1. Titration schedule has to be completed by Visit 03 (Month 3) when all subjects enter the Maintenance Phase.

Procedures & Evaluations:

- Concomitant Medication Log
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Vital Signs (blood pressure, heart rate, temperature, weight)
- Unified Parkinson's Disease Rating Scale (UPDRS) – Parts I, II and III. Only complete UPDRS Part IV if symptomatic therapy has been initiated.
- Assess Need for Symptomatic Therapy (completed only if subject has not reached need for symptomatic therapy)
- Modified Hoehn & Yahr Scale
- Modified Schwab & and England Activities of Daily Living
- Dispense and Titrate study drug (Visit 02 ONLY; see Section 5.2.7)
- Dose Management Log
- Adherence Assessments (see Section 6.3.13)
- Drug Dispensing/Return Log (pill counts)
- Adverse Event Log
- Instructions on blood pressure recording (Visits 01, 02 only) Generate a proceed or not proceed confirmation from BP vendor website**

  **Home blood pressure monitoring can be extended longer at the discretion of the Investigator or following a may not proceed notification from the BP vendor website.

Subjects should be instructed to immediately report any adverse events or changes in medication to the site Investigator or Coordinator.

Record all above activities in source documentation.

6.2.4 Visit 03 (Month 3 +/- 7 days), Visit 04 (Month 6 +/- 7 days), Visit 05 (Month 9 +/- 7 days), Visit 07 (Month 18 +/- 7days) and Visit 09 (Month 30 +/- 7 days)

Procedures & Evaluations:

- Concomitant Medication Log
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Vital Signs (blood pressure, heart rate, temperature, weight)
- Unified Parkinson's Disease Rating Scale (UPDRS) – Parts I, II and III. Only complete UPDRS Part IV if symptomatic therapy has been initiated.

  Assess Need for symptomatic therapy (completed only if subject has not reached need for symptomatic therapy).

  Once the subject initiated symptomatic therapy, UPDRS Part III assessment should be completed in the defined medications OFF state (approximately 12 hours after the last dose of symptomatic therapy) **and** in medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy). Subjects should be instructed NOT to take their PD medications at home on the morning of the study visit. Subjects should be instructed to bring their PD medication to the study visit. Medication should be taken after completion of UPDRS OFF exam. UPDRS Parts 1 and 2 are to be completed in the ON state. Once a subject starts symptomatic therapy, the ON and OFF assessments should be completed for all PD medications including dopamine agonists, MAO inhibitors, or any other dopaminergic therapies.
- Modified Hoehn & Yahr Scale
- Modified Schwab & and England Activities of Daily Living

- Adherence Assessments (see Section 6.3.13)
- Dispense Study Drug (Visits 04, 07 and 09 Only)
- Dose Management Log
- Drug Dispensing/Return Log (pill counts)
- Adverse Event Log

Plasma PK sample will be collected at <u>Visit 03 (Month 3 +/- 7 days) and Visit 04 (Month 6 +/- 7 days)</u>

- Visit should be scheduled in AM as close to 12 hours **post evening dose of the study drug**
- Subjects should be instructed NOT to take their study drug at home on the morning of the study visit.
- Time of the last dose of the study drug should be documented
- Plasma PK sample should be collected (samples should be collected as close to 12 hours post dose as possible) and time of sample collection should be documented
- The subject should take morning dose of the study drug during the visit

- Repeat PK sample should be collected 2-3 hours post dose
- Time of the last dose of the study drug should be documented
- Time of all samples collection should be documented

- **Plasma PK sample will be collected at <u>Visit 04 (Month 6 +/- 7 days),</u>**
- Visit should be scheduled to **occur within 4-8 hours post morning dose of the study drug**
- Subjects should be instructed to take their study drug at home on the morning of the study visit
- Time of the last dose of the study drug should be documented
- Time of the samples collection should be documented

Subjects should be instructed to immediately report any adverse events or changes in medications to the site Investigator or Coordinator.

Record all above activities in source documentation.

6.2.5 Visit 06 – (Month 12 +/- 7 days) and Visit 08 (Month 24 +/-7 days)

<u>Procedures & Evaluations</u>:

- Concomitant Medication Log
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Beck Depression Inventory-II (BDI-II)
- Montreal Cognitive Assessment scale (MoCA)
- Vital Signs (blood pressure, heart rate, temperature, weight)
- Safety Laboratory tests (serum chemistry, hematology, urinalysis)
- Serum pregnancy test - Complete all women unless they are one year postmenopausal or surgically sterile
- Modified Rankin
- Electrocardiogram (12-lead ECG)
- PD Quality of Life Scale (PDQ-39)
- Quality of Life in Neurological Diseases (Neuro-QOL)
- Unified Parkinson's Disease Rating Scale (UPDRS) – Parts I, II, III. Only complete UPDRS Part IV if symptomatic therapy has been initiated.
- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

- Assess Need for symptomatic therapy (completed only if subject has not reached need for symptomatic therapy)

  Once the subject initiated symptomatic therapy, UPDRS Part III assessment should be completed in the defined medications OFF state (approximately 12 hours after the last dose of symptomatic therapy) and in medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy).. Subjects should be instructed NOT to take their PD medications at home on the morning of the study visit. Subjects should be instructed to bring their PD medication to the study visit. Medication should be taken after completion of UPDRS OFF exam. UPDRS Parts 1 and 2 are to be completed in the ON state. Once a subject starts symptomatic therapy, the ON and OFF assessments should be completed for all PD medications including dopamine agonists, MAO inhibitors, or any other dopaminergic therapies.

- Modified Hoehn & Yahr Scale
- Modified Schwab & England Activities of Daily Living
- Dose Management Log
- Adherence Assessments (see Section 6.3.13)
- Drug Dispensing/Return Log (pill count)
- Dispense Study Drug
- Adverse Event Log

Subjects should be instructed to immediately report any adverse events or changes in medication to the site Investigator or Coordinator.

Record all above activities in source documentation.

6.2.6 Telephone Visit T01 (Month 15 +/- 7 days), T02 (Month 21 +/- 7 days), T03 (Month 27 +/- 7 days) and T04 (Month 33 +/- 7 days)

The Telephone Visit T01, T02, T03, or T04 may be conducted by either the study coordinator or investigator.

Procedures & Evaluations:

- Concomitant Medication Log
- Adherence Assessments (see Section 6.3.123
- Adverse Event Log
- Assess Need for symptomatic therapy **(if a subject is determined to need symptomatic therapy over the phone, a Symptomatic Therapy in person office visit should be scheduled before the subject starts therapy. The Investigator must**

conduct the symptomatic therapy treatment assessment at this in person STX visit (see Section 6.2.12).

Subjects should be instructed to immediately report any adverse events or changes in medications to the site Investigator or Coordinator.

Record all above activities in source documentation.

6.2.7 Visit 10/End of Study Drug (EOSD) visit (Month 36 +/- 7 days)

Procedures & Evaluations:

- General Neurological Exam
- General Physical Exam
- Concomitant Medication Log
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Beck Depression Inventory-II (BDI-II)
- Montreal Cognitive Assessment scale (MoCA)
- Vital Signs (blood pressure, heart rate, temperature, weight)
- Safety Laboratory tests (serum chemistry, hematology, urinalysis)
- Serum pregnancy test - Complete all women unless they are one year postmenopausal or surgically sterile
- Plasma sample for storage for future potential biomarker studies (only for subjects who consented for biomarker sampling)
- Modified Rankin Scale
- Electrocardiogram (12-lead ECG)
- PD Quality of Life Scale (PDQ-39)
- Quality of Life in Neurological Diseases (Neuro-QOL)
- Unified Parkinson's Disease Rating Scale (UPDRS) – Parts I, II, III. Only complete UPDRS Part IV if symptomatic therapy has been initiated.
- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Assess Need for symptomatic therapy (completed only if subject has not reached need for symptomatic therapy)

  Once the subject initiated symptomatic therapy, UPDRS Part III assessment should be completed in the defined medications OFF state (approximately 12 hours after the last

dose of symptomatic therapy) and in medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy). Subjects should be instructed NOT to take their PD medications at home on the morning of the study visit. Subjects should be instructed to bring their PD medication to the study visit. Medication should be taken after completion of UPDRS OFF exam. UPDRS Parts 1 and 2 are to be completed in the ON state. Once a subject starts symptomatic therapy, the ON and OFF assessments should be completed for all PD medications including dopamine agonists, MAO inhibitors, or any other dopaminergic therapies

- Modified Hoehn & Yahr Scale
- Modified Schwab & England Activities of Daily Living
- Dose Management Log
- Adherence Assessments (see Section 6.3.13)
- Adverse Event Log
- Taper study drug
- Drug Dispensing/Return Log (pill counts)
- Provide instructions for the drug taper. Subjects will taper their dosage in a blinded fashion to 1 capsule twice a day (equivalent to 5 mg of Isradipine IR or 1 capsule of placebo) every 2 days and stop after that (see Section 5.2.11) Review informed consent and verify that the subject continues to grant consent for retention of DNA and biomarker samples as well their willingness to be contacted for future research

Subjects should be instructed to immediately report any adverse events or changes in medications to the site Investigator or Coordinator.

Record all above activities in source documentation

6.2.8 Visit 11/Final (On Study/ Off Study Drug Evaluation/ Visit 10 + 2 weeks (+ 7 days)

Procedures & Evaluations:

- Concomitant Medication Log
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Vital Signs (blood pressure, heart rate, temperature, weight)
- Review blood pressure records
- Unified Parkinson's Disease Rating Scale (UPDRS) – Parts I, II, III. Only complete UPDRS Part IV if symptomatic therapy has been initiated.

- Assess Need for symptomatic therapy (completed only if subject has not reached need for symptomatic therapy)

  Once the subject initiated symptomatic therapy, UPDRS Part III assessment should be completed in the defined medications OFF state (approximately 12 hours after the last dose of symptomatic therapy) and in medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy).

  Subjects should be instructed NOT to take their PD medications at home on the morning of the study visit. Subjects should be instructed to bring their PD medication to the study visit. Medication should be taken after completion of UPDRS OFF exam. Once a subject starts symptomatic therapy, the ON and OFF assessments should be completed for all PD medications including dopamine agonists, MAO inhibitors, or any other dopaminergic therapies.
- Modified Schwab & England Activities of Daily Living
- Modified Hoehn & Yahr Scale
- Assess primary diagnosis/probability of PD
- Adverse Event Log
- Retrieve all study drug
- Drug Dispensing/Return Log (pill counts)
- Dose Management Log
- Conclusion of Study Participation Form
- Treatment Assignment / Blindedness Questionnaire

  If the subject was previously taking an antihypertensive medication that was adjusted during the study, consult with the subject's PCP or cardiologist prior to readjusting/reinitiating antihypertensive medication if BP elevations are noted. Alternatively, at the Investigator's discretion, (s)he may defer adjustments to the PCP or cardiologist.

Record all above activities in source documentation.

6.2.9 Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the site Investigator. The date and reason for the unscheduled visit will be recorded in the source documentation.

In most cases, an unscheduled visit will be warranted due to an adverse event, or a significantly abnormal lab value.

Procedures & Evaluations:

- Concomitant Medication Log
- Vital Signs (blood pressure, heart rate, temperature, weight)
- Safety Laboratory tests (serum chemistry, hematology, urinalysis) *if clinically indicated*
- Instructions on blood pressure recording (if clinically indicated)
- Generate a proceed or not proceed confirmation from BP vendor website, if applicable
- Dose Management Log (if study medicine adjustment required)
- Adherence Assessments (see Section 6.3.13)
- Adverse Event Log

  If Unscheduled visit occurs during study drug titration and due to the need to reduce antihypertensive medications, this visit should include all V01 procedures and evaluations.

Record all above listed activities in source documents.

6.2.10 Symptomatic Treatment Visit

> If the site Investigator determines that a subject needs PD symptomatic treatment, the subject must come in for a PD symptomatic treatment visit. **Subjects who initiate symptomatic therapy will continue in the study on study drug and continue follow up until the Final visit. The Symptomatic Therapy Visit should occur before a subject starts PD symptomatic therapy. Once the subject initiates symptomatic therapy, UPDRS Part III assessment should be completed in the defined medications OFF state (approximately 12 hours after the last dose of symptomatic therapy) and in medications ON state (based on the subject/investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy). UPDRS Parts 1 and 2 are to be completed in the ON state. Once a subject starts symptomatic therapy, the ON and OFF assessments should be completed for all PD medications including dopamine agonists, MAO inhibitors, or any other dopaminergic therapies**

If the symptomatic treatment visit occurs within the window of a regularly scheduled study visit, the symptomatic treatment visit will be completed in place of the regularly scheduled study visit. **If this visit is conducted *in place of* the regularly scheduled V06, V08 and V10, visit assessments will include the following assessments: safety labs, pregnancy test[6], ECG, drug dispensing/titration.**

Procedures & Evaluations:

- Concomitant Medication Log

- Montreal Cognitive Assessment scale (MoCA)
- Beck Depression Inventory II (BDI-II)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Vital Signs (blood pressure, heart rate, temperature, weight)
- Modified Rankin scale
- PD Quality of Life Scale (PDQ-39)
- Quality of Life in Neurological Diseases (Neuro-QOL)
- Unified Parkinson's Disease Rating Scale (UPDRS) – Parts I, II, and III.
- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Modified Hoehn & Yahr Scale
- Modified Schwab & England Activities of Daily Living
- Dose Management Log (if study medicine adjustment required)
- Adherence Assessments (see Section 6.3.13)
- Adverse Event Log

Record all above listed activities in source documents.

Initiation of symptomatic therapy is a reportable event and should be reported to CTCC. The subjects should remain in the study on their initial study drug assignment.

6.2.11 Premature Withdrawal Visit (PW)

Subjects have the right to withdraw from the study at any time without prejudice. In the event of premature study withdrawal (either subject or Investigator initiated), a Premature Withdrawal visit should occur. **All efforts should be made to conduct the PW visit prior to study drug discontinuation.**

Reasons for withdrawal of the subject prior to completion of the study must be stated in the CRF and in the site source documentation for all study subjects who were enrolled in the study. ***The CTCC must be informed by telephone within 24 hours of all study subjects who are withdrawn from the study.***

At the time of the premature withdrawal visit, subjects should be instructed to taper their study drug if applicable. Subjects will taper their dosage by 5 mg of Isradipine IR or placebo to one capsule twice daily every 2 days). If a subject has already decreased their dosage due to prior intolerability to 5mg or below, then they will discontinue the drug at the start of the taper. The subject should be instructed to take the study drug (with or without food) in the morning () and in the evening.

Written directions for drug tapering should be given to the subject. Visit 11 activities should be performed at that time.

Every effort should be made to keep each subject in the study. Subjects coming off study drug should be encouraged to continue in the study, off study drug. However, all subjects must present for a final (V10 or PW) in-person visit.

Procedures & Evaluations:

- General Neurological Exam
- General Physical Exam
- Concomitant Medication Log
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Beck Depression Inventory II (BDI-II)
- Montreal Cognitive Assessment scale (MoCA)
- Assess primary diagnosis/probability of PD
- Vital Signs (blood pressure, heart rate, temperature, weight)
- Safety Laboratory tests (serum chemistry, hematology, urinalysis)
- Plasma PK sample - To be done only if premature withdrawal corresponds to Visits 3 or 4 (see instructions Section 6.2.4)
- Plasma sample for storage for future potential biomarker studies (only for subjects who consented for biomarker sampling)
- Serum pregnancy test - Complete all women unless they are one year postmenopausal or surgically sterile
- Modified Rankin Scale
- Exercise Questionnaire
- Electrocardiogram (12-lead ECG)
- PD Quality of Life Scale (PDQ-39)
- Quality of Life in Neurological Diseases (Neuro-QOL)
- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Unified Parkinson's Disease Rating Scale (UPDRS) – Parts I, II, III. Only complete UPDRS Part IV if symptomatic therapy has been initiated.
- Assess Need for symptomatic therapy (completed only if subject has not reached need for symptomatic therapy)

Once the subject initiated symptomatic therapy, UPDRS Part III assessment should be completed in the defined medications OFF state (approximately 12 hours after the last dose of symptomatic therapy) and in medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy). Subjects should be instructed NOT to take their PD medications at home on the morning of the study visit. Subjects should be instructed to bring their PD medication to the study visit. Medication should be taken after completion of UPDRS OFF exam. UPDRS Parts 1 and 2 are to be completed in the ON state. Once a subject starts symptomatic therapy, the ON and OFF assessments should be completed for all PD medications including dopamine agonists, MAO inhibitors, or any other dopaminergic therapies

- Modified Hoehn & Yahr Scale
- Modified Schwab & England Activities of Daily Living
- Dose Management Log
- Adherence Assessments (see Section 6.3.13)
- Adverse Event Log
- Provide written instructions for the drug taper.
- Retrieve all study drug, if subject is no longer taking drug at the time of PW visit. Otherwise retrieve all study drug at time of Premature Withdrawal Follow-up Visit
- Drug Dispensing/Return Log (pill counts)
- Treatment Assignment / Blindedness Questionnaire - Complete if subject is no longer taking drug at time of PW visit. Otherwise, complete questionnaires at time of Premature Withdrawal Follow-up Visit

Record all above activities in source documentation.

6.2.12 Premature Withdrawal Follow-up Visit

All subjects who are on study drug at the time of the PW visit should have a visit approximately two weeks after the premature withdrawal visit and after the study drug has been tapered off. As this visit is primarily for the purposes of monitoring subject safety, subjects who withdraw consent should also be asked whether they agree to attend this visit for safety checks and follow-up.

Any new AEs reported at this visit must also be reported in the CRF and must be followed for 30 days from this visit or until resolution, whichever occurs first.

Procedures & Evaluations:

- Concomitant Medication Log
- Columbia Suicide Severity Rating Scale (C-SSRS)

- Vital Signs (blood pressure, heart rate, temperature, weight)
- Review blood pressure records. If the subject was previously taking an antihypertensive medication that was adjusted during the study, consult with the subject's PCP or cardiologist prior to readjusting/reinitiating antihypertensive medication if BP elevations are noted. Alternatively, at the Investigator's discretion, (s)he may defer adjustments to the PCP or cardiologist.
- Adverse Event Log
- Retrieve all study drug, if drug not retrieved at PW visit
- Drug Dispensing/Return Log (pill counts), if drug not retrieved at PW
- Dose Management Log
- Conclusion of Study Participation Form
- Treatment Assignment / Blindedness Questionnaire, if not completed at PW

The following assessments should be completed if they were not completed at the PW visit:

- Unified Parkinson's Disease Rating Scale (UPDRS) – Parts I, II, III. Only complete UPDRS Part IV if symptomatic therapy has been initiated.
- Assess Need for symptomatic therapy (completed only if subject has not reached need for symptomatic therapy)

  Once the subject initiated symptomatic therapy, UPDRS Part III assessment should be completed in the defined medications OFF state (approximately 12 hours after the last dose of symptomatic therapy) and in medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy).. Subjects should be instructed NOT to take their PD medications at home on the morning of the study visit. Subjects should be instructed to bring their PD medication to the study visit. Medication should be taken after completion of UPDRS OFF exam. UPDRS Parts 1 and 2 are to be completed in the ON state.

- Modified Schwab & England Activities of Daily Living
- Modified Hoehn & Yahr Scale

Record all above activities in source documentation.

6.2.13 Adverse Event Follow-up Visit

All subjects who have unresolved adverse events or SAEs at the time of their final study visit (Visit 11 or Premature Withdrawal Follow Up visit) should have a phone call approximately 30 days after their final study visit. The purpose of this phone call is to assess the final outcome of the unresolved AEs as either resolved or on-going.

This phone call is not required for subjects whose AEs were resolved prior to at the time of the final study visit.

Procedures & Evaluations:

- Adverse Event Log
- Conclusion of Study Participation Form

6.3 Special Instructions and Definitions of Evaluations

6.3.1 Informed Consent

This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50. The CTCC must be given an opportunity to review the consent form prior to site IRB/REB submission and before it is used in the study.

In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, together with any potential hazards/risks must be read and/or explained to each subject. Each subject will sign such an informed consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record. The subject must be assured of the freedom to withdraw from participation in the study at any time.

It is the Investigator's responsibility to make sure that the subject understands what she/he is agreeing to and that written informed consent is obtained before the subject is involved in any protocol-defined procedures including screening procedures. It is also the Investigator's responsibility to retain the original signed consent form and provide each subject with a copy of the signed consent form.

6.3.2 Documentation of Parkinson Disease

The diagnosis of idiopathic PD should be documented based on the UK brain bank diagnostic criteria[47]. The subjects are expected to have at least two out of three cardinal manifestations of PD. If tremor is not present, subjects must have unilateral onset and persistent asymmetry of the symptoms.

6.3.3 Medical History- will utilize NIH common data elements form *http://www.commondataelements.ninds.nih.gov/*

The form should focus on significant medical history of all problems or conditions other than those related to the focus of the study and are presented in the order typically used

during a subject visit. If the subject reports more than one medical condition per system, record each condition on a separate line.

6.3.4 PD Treatment History

Treatment history will be reviewed and recorded at the screening visit on the Concomitant Medication Log. All PD treatment taken up to 90 days prior to the Baseline visit should be recorded.

6.3.5 Concomitant Treatments

Concomitant medications will be reviewed and recorded at screening and reviewed for accuracy at each study visit and amended as necessary. All medications taken up to 90 days prior to the Baseline visit should be recorded.

6.3.6 Study Intervention Modification

Any change in the study drug dose should be captured on the Dose Management Log

6.3.7 Exercise Questionnaire

Subjects will be asked to complete the Exercise Questionnaire at the Baseline visit, or once the subject consents, and at their final visit (Visit 11 or PW). This scale asks about mild to strenuous exercise and includes factors to include minutes per week. See Section 6 of the Operations Manual for additional details on this assessment.

6.3.8 Mini Environmental Risk Questionnaire (MERQ)

Exposure to risk factors of interest (pesticides, chemicals, heavy metals, caffeine use, smoking history and concomitant medication use) will be assessed using a self-reporting questionnaire. This questionnaire will be completed at the Baseline visit, or once the subject consents, and at the final visit (Visit 11 or PW). See Section 6 of the Operations Manual for additional details on this assessment.

6.3.9 Clinical Assessments

The study will use NINDS Common Data Elements in developing the CRFs http://www.commondataelements.ninds.nih.gov/).

Efficacy Assessments

1. Unified Parkinson Disease Rating Scale (UPDRS)

   Will use the NINDS Common Data Elements UPDRS CRFs (see http://www.commondataelements.ninds.nih.gov/).

   The Unified Parkinson Disease Rating Scale (UPDRS) is a widely used and well-studied clinical rating scale for assessing the progression of disability in PD. The

reliability, validity and factor structure of the UPDRS have been extensively studied [48-50]

The scale has three components, each consisting of questions answered on a 0-4 point scale. Part I assesses mentation, behavior and mood; Part II assesses activities of daily living in the week prior to the designated visit; Part III assesses motor abilities at the time of the visit; Part IV assesses complications of therapy (motor fluctuations, dyskinesia, etc) A total of 31 items are included in Parts I, II and III. Each item will receive a score ranging from 0 to 4 where 0 represents the absence of impairment and 4 represents the highest degree of impairment.

Subjects will be assessed by the Investigator or Coordinator on Parts I and II. The Investigator must assess Part III of the UPDRS. The sum of Parts I, II and III at each visit will provide a total UPDRS score. Both the primary and secondary endpoints will be based on changes from the Baseline Visit in total UPDRS scores. UPDRS Part IV will be completed only on the subjects who have reached the endpoint and were started on symptomatic therapy.

The same Investigator or Coordinator should assess the subject on the UPDRS (and other site Investigator specific study evaluations) at all study visits. **The motor portion of the UPDRS must be completed by the Investigator.** Once the subject initiated symptomatic therapy, UPDRS Part III assessment should be completed in the defined medications OFF state (approximately 12 hours after the last dose of symptomatic therapy) and in medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy). UPDRS Parts 1 and 2 are to be completed in the ON state. Once a subject starts symptomatic therapy, the ON and OFF assessments should be completed for all PD medications including dopamine agonists, MAO inhibitors, or any other dopaminergic therapies

- Subjects should be instructed NOT to take their PD medications at home on the morning of the study visit. Subjects should be instructed to bring their PD medication to the study visit. Medication should be taken after completion of UPDRS OFF exam.

2. MDS-UPDRS

U*se of the MDS-UPDRS is recommended in the NINDS Common Data Elements (see http://www.commondataelements.ninds.nih.gov/).*

The *Movement* Disorder Society (MDS)-sponsored new version of the UPDRS is founded on the critique that was formulated by the Task Force for Rating Scales in Parkinson's disease (*Mov Disord* 2003;18:738-750).

MDS version of the UPDRS maintains the overall format of the original UPDRS, but addresses issues identified in the critique as weaknesses and ambiguities.
The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living, Part III (motor examination) and Part IV (motor complications). Part I has two components: IA concerns a number of behaviors that are assessed by the Investigator with all pertinent information from subjects and caregivers, and IB is completed by the subject with or without the aid of the caregiver, but independently of the Investigator. These sections should however, be reviewed by the Investigator or Coordinator to ensure that all questions are answered clearly and the Investigator or Coordinator can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but should be reviewed by the Investigator or Coordinator to ensure completeness and clarity. Of note, the official versions of Part IA, Part IB and Part II of the MDS-UPDRS do not have separate on or off ratings. However, for individual programs or protocols the same questions can be used separately for on and off. Part III has instructions for the Investigator to give or demonstrate to the subject; it is completed by the Investigator. Once the subject initiated symptomatic therapy, the MDS-UPDRS assessments will be completed in the medication ON state only. Part IV has instructions for the Investigator or Coordinator and also instructions to be read to the subject. This part integrates subject-derived information with the assessor's clinical observations. The current study will request that the MDS-UPDRS be completed in the medication ON state, if applicable.

- The same Investigator or Coordinator should assess the subject on the MDS-UPDRS (and other site Investigator specific study evaluations) at all study visits. **The motor portion of the MDS-UPDRS must be completed by the Investigator.**

3. Modified Hoehn & Yahr Scale

The Modified Hoehn & Yahr Scale [51] is an 8-level Parkinson's disease staging instrument. This Investigator assessment will be done at each scheduled visit. Subjects with a Modified Hoehn & Yahr score of 3 or greater at the Baseline Visit will be excluded from participation in the study.

4. Modified Schwab & England Independence Scale

The Modified Schwab & England scale [52] is an Investigator and subject assessment of the subject's level of independence at all scheduled study visits. The subject will be scored on a percentage scale reflective of his/her ability to perform acts of daily living in relation to what he/she did before Parkinson's disease appeared. Scores with associated descriptors range in increments of 10% to 100% for normal (subject has full ability and is completely independent; essentially normal), to 0% (vegetative functions such as swallowing, bladder and bowel func-

tions are not functioning; bedridden). Scores should be coded in increments of 5, (i.e. 095, 090, and 085).

5. Beck Depression Inventory II (BDI-II)

Will use *the NINDS Common Data Elements CRFs (see http://www.commondataelements.ninds.nih.gov/).*

The Beck Depression Inventory (BDI-II) is a validated self-reported 21- item depression scale that was tested and validated as a reliable instrument for screening for depression in PD [53]. Subjects will complete the BDI-II at the Screening, the symptomatic treatment visit, Visits 06 and 08 and EOSD (V10) or Premature Withdrawal Visits. Subjects who score above 15 at screening will be excluded from participation in the study and referred for further evaluation and possible treatment. If score at any point in study the BDI score is above 15, appropriate assessment and treatment should be conducted.

6. Montreal Cognitive Assessment

Will use the NINDS Common Data Elements MoCA CRFs (see http://www.commondataelements.ninds.nih.gov/).

The Montreal Cognitive Assessment (MoCA) is a brief 30-point screening instrument that was developed and validated to identify subjects with mild cognitive impairment (MCI) [3]. The MoCA has a sensitivity of 90% in detecting MCI compared to MMSE sensitivity of 18%. MoCA includes more items aimed at detecting frontal executive dysfunction and visuospatial processing dysfunction compared to MMSE. The MoCA is now widely used and shown to be a more sensitive tool for screening for cognitive impairment in PD [2, 54]. MoCA was given one of the highest rankings (best) by NINDS CDE among the brief cognitive assessment tools in PD.

If the subject has 12 years of education or fewer, a point is added to his/her total score. Note that this number of years does not refer to a particular education level, for example, it does not refer to individuals that have or have not completed high school. The number of years of education must actually be counted starting after kindergarten (kindergarten must not be included in the count). Please note that the maximum score is 30, therefore, if a subject scores 30/30, a point is not added if he/she has 12 years of education or less.

7. The Modified Rankin scale

The Modified Rankin Scale (mRS)[van Swieten et. al., 1988] is a widely used measure of overall functional disability. It has been used as a as a functional outcome measure in stroke and multiple sclerosis [Burn, 1992; Sulter et. al., 1999;

Wilson et. al., 2002; Wilson et. al., 2005; Shinohara et. al., 2006]. The Modified Rankin scale scores range from 0 to 6 with a higher score correlating with higher level of disability.

8. Columbia Suicide Severity Rating Scale (C-SSRS)

As required by the FDA, study subjects will be screened for suicidality (suicidal behavior or ideation) at screening and at each subject visit. Certified Investigator or Coordinator will use the Columbia Suicide Severity Rating Scale (C-SSRS) [55] (*http://www.cssrs.columbia.edu)*

The Columbia Suicide Severity Rating Scale is a structured interview developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and monitor suicidal events during a treatment period. The interview can provide an overall assessment of suicidal ideation as well as behavior in order to generate a summary measure of suicidality. This rating scale has been used in prior interventional studies for both psychotropic and non-psychotropic compounds over the past four years. This assessment will be administered during the Screening visit to exclude subjects with active suicidality and at all scheduled in-person study visits. Additionally, this assessment will be administered as clinically indicated at Unscheduled visits and in the setting of any suicide attempt to ensure that the reporting of suicidality and suicide attempts is consistent across study centers. Decisions about continued study participation of subjects found to be suicidal will be made collaboratively by the site Investigator, Principal Investigator, and CTCC Clinical Monitor The site Investigator will make a referral to psychiatrist or other Mental Health Care professional, as appropriate.

9. PD Quality of Life Questionnaire

PD Quality of Life Scale (PDQ-39). PDQ-39 is recommended by the *NINDS Common Data Elements CRFs (see http://www.commondataelements.ninds.nih.gov/).*

The questionnaire asks the subject to evaluate how PD has affected their health and overall quality of life at that point in time. The total quality of life scale includes subscales relating to social role, self-image/sexuality, sleep, outlook, physical function and urinary function.

10. Quality of Life in Neurological Diseases (Neuro-QOL http:www.neuroqol.org

Neuro-QOL is a set of self-reported measures that assess the health-related quality of life of persons with neurological disorders. The quality of life scale includes measures for anxiety, depression, upper extremity function (fine motel, ADL), lower extremity function (mobility), applied cognition (executive function and general concerns), positive affect and well-being and stigma. The questionnaire asks the subject to evaluate their quality of life in the past 7 days. The Neuro-QOL questionnaires are currently available in Spanish but not French translation. French-speaking study subjects will not be completing these questionnaires.

6.3.10 Laboratory Evaluations

Clinical laboratory tests will be performed by a central laboratory specified and the laboratory's reference ranges will be used. The CTCC must be notified by the central laboratory during the study of any changes to the reference ranges. All samples for laboratory analysis must be collected, prepared, labeled, and shipped according to the laboratory's requirements. (Refer to instructions of the laboratory's manual.)

Blood samples will be collected at the Screening visit, Visits 06 and 08, and V10 (EOSD) or Premature Withdrawal Visit and Unscheduled visits (if clinically indicated) for the standard clinical safety laboratory analyses noted below. Retests may be performed if needed between visits for questionable results.

Clinical laboratory test results will be forwarded to individual Investigators and to the CTCC.

Clinical Laboratory Tests

Clinical Chemistry – albumin, alkaline phosphatase, aspartate transaminase (SGOT; AST), alanine transaminase (SGPT; ALT), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), phosphate, potassium, sodium, total bilirubin, total creatine kinase (creatine phosphokinase), total protein, uric acid

Hematology – Hemoglobin, hematocrit, red blood cell count (RBC), platelet count, white blood cell count (WBC) with differential count (bands, monocytes, neutrophils, eosinophils, lymphocytes, basophils)

Urinalysis – pH, protein, glucose, ketone, blood microscopic, WBC count, RBC count, casts

Pregnancy Tests - Serum pregnancy test at Screening, Visits 06 and 08 and V10 (EOSD) or Premature Withdrawal Visits and Unscheduled visits (if clinically indicated). Preg-

nancy testing should be done for all women unless they are one year postmenopausal or surgically sterile. ***Any subject becoming pregnant during the study will be tapered from the study drug immediately. In addition, all attempts will be made to follow the subject until delivery.*** Any pregnancy that occurs during the study must be reported to the CTCC.

Laboratory reports from the central laboratory will be signed and dated by the site Investigator following review, and filed with the subject's source documents.

PK samples

Plasma PK samples will be collected at the Screening visit, Visits 03 (3 months) and 04 (6 months), or Premature Withdrawal Visit if it corresponds to Visits 03 or 04. The objective of collecting blood PK samples is to confirm isradipine trough concentrations and to establish a sparse PK profile of Isradipine IR based on the samples collected at 2-3 and 4-8 hours post dose windows. The data will be analyzed to demonstrate an appropriate level is achieved for the formulation used in this study and to address high inter-patient variability in serum concentrations to support the analysis in case variable results were observed. PK samples will be collected as outlined in Section 6.2.4 and shipped according to the laboratory's requirements. (Refer to instructions in the laboratory's manual.)

Plasma Biomarker samples

A blood sample will be collected from each subject at Screening, Month 36 (V10/EOSD) visits or at Premature Withdrawal visit and stored. These samples may be shared with other researchers for future unspecified research. Subjects will be given the option of refusing to have this sample collected, and their decision will not affect their participation in the study.

DNA Sample Collection

A blood sample will be collected from each subject at Screening and stored. These samples will be used to extract DNA for storage and shared for future unspecified research. Subjects will be given the option of refusing to have this sample collected or may request that their sample be destroyed at any time, without affecting their participation in the study. One of the rationales for the DNA sample collection is to assess if there is correlation of response to isradipine with a particular genetic profile.

6.3.11 Electrocardiogram (ECG)

A 12-lead resting ECG will be performed utilizing the central ECG laboratory equipment at Screening Visit, Visits 06, 08 and at the V10 (EOSD) or Premature Withdrawal visits. ECG will also be conducted at the Symptomatic Therapy visit if this visit is conducted in place of a regularly scheduled V06, V08 or V10. ECG readings/results will be provided by the Centralized cardiologist's interpretation.

Presence of 2nd or 3rd degree atrioventricular block will exclude the subjects from participation in the study. Investigator may consider other significant ECG abnormalities as the reason for exclusion for participation in study.

6.3.12 Additional Evaluations

Assess need for Symptomatic Treatment:
At each visit (except baseline), the Investigator will assess the subject's need for symptomatic treatment. A questionnaire will be used to facilitate the Investigator's decision. This decision will be based on PD disability posing a threat to the subject's current occupational status, current abilities (potential capacities) related to occupational matters, to handle routine personal finances and domestic responsibilities, and activities of daily living.

6.3.13 Adherence Assessments

At each study visit, the site Investigator and/or Study Coordinator will assess the subject's adherence with the study requirements. This will include checks of protocol compliance, concomitant medication use, blood pressure recordings, and use of study drug in order to assess the reliability of subject-generated data. In extreme circumstances, subjects who consistently fail to comply with the study requirements may be withdrawn from the study.

6.3.14 Treatment Assignment / Blindedness Questionnaire

Subjects and Investigators will be asked to complete the Treatment Assignment/ Blindedness Questionnaire during the V11 Final visit or Premature Withdrawal Visit. The Blindedness Questionnaire will be used to assess subject's and Investigator's perception of the knowledge of their group assignment to placebo versus active treatment.

7 MANAGEMENT OF ADVERSE EVENTS

7.1 Isradipine Side Effect Profile

Isradipine IR is a dihydropyridine Ca^{2+} channel antagonist that is FDA approved for treatment of hypertension since 1990 *(http://www.drugs.com/pro/isradipine.html)*.

The side effect profile of Isradipine IR is related to the primary mechanism of action of the agent as a vasodilator of the vascular smooth muscles and myocardium, and includes hypotension, bradycardia, weakness, and syncope. The most common adverse effect is peripheral edema as reflection of the vasodilatory effect of the agent. The other side effects include angina, asthenia, flushing, heart failure, palpitations, and dizziness. According to the package insert, the adverse effects are usually not serious, dose dependent, and respond well to dose reduction or discontinuation of therapy.

Isradipine has no effect on atrioventricular or sinoatrial conduction. The only absolute contraindications for Isradipine IR are hypersensitivity to dihydropyridine compounds and hypotension defined as systolic blood pressure below 90 mm Hg. Isradipine IR should be used with caution in subjects with bradycardia. Subjects with clinically significant bradycardia will be excluded from the study.

Below is a list of most common potential Isradipine IR related adverse events from the drug package insert *(http://www.drugs.com/pro/isradipine.html)* .(See Table 4 and 5 above for list of adverse events.)

The adverse effects associated with isradipine generally are not serious and respond well to either dosage reduction or discontinuation of therapy. Most adverse effects during isradipine therapy are related to vasodilatory actions and, in many cases, are dose-related.

The most common cardiovascular adverse effect attributed to isradipine therapy is peripheral edema, which is a reflection of the potent vasodilatory effect of isradipine, although it occurs less frequently than with nifedipine. Peripheral edema may be an indicator of worsening congestive heart failure, but it more commonly is due to peripheral vasodilation.

Although calcium-channel blockers are effective in treating angina, worsening of angina has occurred in as many as 10% of patients receiving isradipine for angina pectoris. This effect may be caused by excessive hypotension, coronary steal, or reflex sinus tachycardia (rare with isradipine). In rare cases, myocardial infarction has occurred but could not be attributed solely to the drug and may have been only a reflection of disease progression. Patients with angina should be observed for worsening symptoms when isradipine therapy is begun, particularly if beta-blocker therapy is being withdrawn.

Other common side effects of isradipine, primarily related to vasodilation, include flushing, weakness or asthenia, fatigue, headache, syncope, hypotension, palpitations, dizziness, and lightheadedness.

Less common but potentially serious adverse effects of isradipine include angioedema, dyspnea, wheezing (especially if underlying respiratory disease or pulmonary edema exists), vertigo, and visual disturbances.

Gynecomastia has been associated with the use of calcium channel blockers.

8 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

The study is designed as a randomized Phase 3, 2-arm, double-blind, parallel group trial with subjects randomized to Isradipine IR 5 mg or matching placebo twice daily.

Primary efficacy analysis will be performed after all subjects complete 36 months on their randomized treatment assignment. We expect that nearly all subjects will require symptomatic therapy (e.g., levodopa or dopamine agonist) prior to the end of the 36

months study; if so they will still continue on their randomized treatment assignment in conjunction with the symptomatic therapy. In that case the primary statistical analysis will be based on UPDRS assessed in the medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy).

Primary efficacy variable

The primary efficacy measure is the change in the total UPDRS score in the active treatment arm versus placebo between the baseline and 36 months. In order to provide assurance that any differences between the treatment groups in the primary outcome measure are not due to differences in the usages of symptomatic medication, current and cumulative dosages of symptomatic medication at the 36-month visit will also be compared, using accepted levodopa dose equivalency formulas[1] We will also repeat our UPDRS analyses after stratification by medication status (dosage of symptomatic treatment calculated as the levodopa equivalent dose). We will also perform exploratory analyses along the lines suggested by Holford and Nutt[56], based on flexible models of both short term symptomatic effects and long-term disease-modifying effects of treatment.

Secondary efficacy measure

The study secondary objectives are to explore long-term efficacy of Isradipine IR 5 mg twice daily to slow progression of disability between the baseline and 36 months of treatment as measured by parameters that reflect long term disability in PD:

1) Motor function (characterized by UPDRS Part III OFF score, UPDRS ambulatory capacity subscore, time to initiation of symptomatic therapy, time to onset of motor complications, dose and utilization of symptomatic therapy)
2) Cognitive function as measured by MoCA
3) Global measures of disability as measured by modified Rankin score
4) Measures of functional status and quality of life (PDQ-39, modified Schwab and England, MDS-UPDRS Motor and Non-Motor Experience of Daily Living)

Interim tolerability analysis

An interim tolerability analysis will be performed after the first 60 subjects complete the titration period of the study (Visit 03 (Month 3). Tolerability will be defined as ability to achieve and maintain target daily dosage of study drug (10 mg) by the end of titration period. The tolerability threshold will be defined as more than 30% difference in the tolerability of the active treatment group relative to the placebo group. Only dosage reductions, discontinuations, and premature terminations due to intolerability will be included in the analysis, terminations for other reasons will not be included in this analysis. The study may be terminated if tolerability parameters are not met. These analyses will be conducted by the unblinded statistician and reported to the DSMB.

Interim analysis of the Pharmacokinetic (PK) data

An interim PK analysis will be performed (at steady-state) after the first 60 subjects who reach target daily dose of 10 mg complete the titration phase of the study to assure that serum concentrations fall within predicted range. Cmin and Cmax serum concentrations

will be analysed. Only data on the subjects who have reached 10mg dose of study drug (Isradipine IR or placebo) will be included in the interim analysis. Based on the data discussed in Section 2.1, we expect the Cmin concentration to be 0.4±0.2 ng/ml (1 SD from the Cmin mean). Thus Cmin = 0.2 ng/ml should be established as the threshold of the therapeutic effect. In case mean Cmin concentrations fall below 0.2 ng/ml, the following paradigm is proposed:

1) May validate the PK data by completing a full PK profile on a small sample of study subjects (N=6)
2) In case the AUC 0-12hr falls within the expected range (13.9± 6.1 ng/ml)(Holmes and Kutz 1993), the study will proceed as planned
3) In case AUC 0-12hr is below expected range the DSMB may seek independent assessment of the PK data by a clinical pharmacologist
4) In case the Cmin values are below Cfloor (0.25 nM (0.098 ng/ml)) – DSMB may consider an alternative dosing regimen

Interim futility and efficacy analysis

An interim analysis for futility and efficacy will be performed after primary outcome data are available for the first 168 subjects (50%) to enroll in the study. The study may 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 if the recruitment rate falls below that projected, the interim analysis may be brought forward and performed as soon as the first 30% of the subjects to enroll have completed (or terminated). In that case a second interim analysis for futility will be conducted on the first 75% of subjects to enroll.

These analyses will be conducted by the unblinded statistician and reported to the DSMB. 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.

8.2 Outcomes

8.2.1 Primary Outcome

Efficacy:

Efficacy will be defined as the change in total UPDRS score between the baseline visit and month 36. Comparison will be made between active treatment arm and placebo. We expect that nearly all subjects will require symptomatic therapy (e.g. levodopa or dopamine agonist) prior to the end of the 36 months study. In that case UPDRS will be assessed in the medications ON state (based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy).

Medications ON state was chosen based on the following rationale: if disease modifying effect of isradipine exists it will be sustained even in the medications ON state; the practical difficulty in withdrawing subjects; the persistent symptomatic benefit of symptomatic therapy even in the "defined medications OFF" state. In addition there are no pilot data on the longitudinal change of UPDRS in the medications OFF state over 36 months period in de novo population to allow power calculations.

Our primary efficacy analysis will use analysis of covariance applied to the change from baseline in the total UPDRS score. The baseline value will be entered into the model as a continuous variable, the assigned treatment and the enrolling Investigator will be entered as a stratification variable. The primary analysis will be based on the intent-to-treat principle and will include all subjects who have 36 month data. A two-sided test with alpha = 0.05 will be used to declare statistical significance. Sensitivity analyses will be performed using data values imputed under various "missingness" mechanisms for the subjects who do not complete 36 months of follow-up. Consistency of results over study sites and with respect to major demographic and clinical baseline variables will be assessed descriptively and by appropriate tests of statistical interaction. We will also perform an exploratory analysis by achieved final dosage (0, 2.5, 5.0, 7.5 and 10.0) for the subjects assigned to active treatment.

8.2.2. Secondary Outcomes

Efficacy analysis (at 36 months):
The change in the following measures of disability from baseline to 36 months will be analyzed:

I. <u>Motor disability</u>
   a. The change in UPDRS Part III Motor subscale in the defined medications OFF state (approximately 12 hours after the last dose of symptomatic therapy for those subjects that have initiated symptomatic therapy)
   b. MDS-UPDRS Motor score in the defined medications ON state (as per the primary outcome)
   c. The change in the ambulatory capacity (sum of 5 UPDRS questions: falling, freezing, walking, gait, postural stability)
   d. Time to initiation of symptomatic therapy
   e. Proportion of subjects that start symptomatic therapy
   f. Analysis of symptomatic therapy utilization as measured by levodopa equivalence dose[1]
   g. Time to onset and severity of motor complications as measured by UPDRS IV subscale (complications of therapy) for those subjects that have initiated symptomatic therapy

   For continuous measures, the analysis will proceed in the same way as for the primary outcome measure. Logistic regression will be used for the binary out-

come (e) and Cox's proportional hazards model for the time-to-event outcomes (d) and (g).

II. Cognitive disability
   a. The change in the cognitive function as measured by the change in the MoCA [2, 3]

III. Measure of global disability
   a. The change in the Modified Rankin score

IV. Measures of functional status and quality of life
   a. The change in Activities of Daily Living (ADL) subscale of the UPDRS
   b. The change in the MDS-UPDRS Part II
   c. The change in the modified Schwab and England scale
   d. The change in Parkinson Disease Quality of Life Questionnaire-39 (PDQ-39) [4]
   e. The change in Neuro-QOL
   f. The change in Non-motor and Motor Experiences of Daily Living scores of the MDS-UPDRS

While the primary outcome measure at 36 months is the change in the total UPDRS we also will explore the measures that reflect long term disability in PD including motor and cognitive function as well as global measures of disability and quality of life measures (as outlined below) between the baseline and 36 months of treatment. While 36 months is not a sufficiently long period of time to assess the impact of an intervention on such long term measures of PD disability as gait, balance, and cognitive function; the current analysis may provide a signal of efficacy that may be followed by a long term confirmatory study . We will also examine whether onset of disability requiring symptomatic treatment and early changes in total UPDRS and its components are useful predictors of long-term disability.

Safety and Tolerability Analysis:

1. The ability to complete the 36 months study on the originally assigned treatment dosage
2. The proportion of subjects requiring dosage reductions secondary to intolerability
3. The frequency of adverse events and serious adverse events
4. Laboratory and ECG abnormalities
5. An interim tolerability analysis will be performed after the first 60 subjects complete titration period of the study (Visit 03) as discussed in section 9.1

All subjects known to have received study treatment will be included in the safety analysis.

All adverse events and abnormal laboratory values results will be listed by treatment and be identified by subject and site. They will also be tabulated by treatment group, severity and perceived relationship to study drug. Fisher's exact test will be used to compare each

active treatment group to the placebo group with regard to the proportion of subjects experiencing a particular adverse event. Separate analyses will be performed excluding mild events and those categorized as unrelated to study drug. In all comparative analyses, events occurring after Baseline Visit will not be counted if the subject experienced the event at the Baseline Visit, unless the severity increases.

A similar approach will be adopted to compare out-of-range laboratory values between groups.

The following measures of the effect of the study drug on vital signs, specifically on orthostatic blood pressure will be analyzed:

- Changes in vital signs recorded at each visit.
- The proportions of subjects who develop orthostatic hypotension as defined by a drop in systolic blood pressure of greater than or equal 20 mm Hg and a drop in diastolic blood pressure of greater than or equal to 10 mm Hg when going from a sitting to a standing position.
- The proportions of subjects who develop symptomatic orthostatic hypotension, defined as orthostatic blood pressure changes, as defined previously, associated with presence of positional dizziness or other symptoms.

Comparisons of the active treatment group with the placebo will be made using one-sided Fisher's exact tests supplemented by tests of trend in proportions to examine exposure-response relations among the four groups.

Exploratory analysis:

An analysis of the correlation between clinical efficacy measures and plasma PK concentrations will be performed. The analysis will be based on correlation of the change of the efficacy measures and serum concentration of isradipine measured as AUC 0-12 hour based on the sparse PK profile collected during the study.

8.3 Sample Size and Accrual

The key issues in the determination of sample size are the variability of the primary outcome measure and the magnitude of the treatment effect one wishes to detect.
As regards the former, there are several sources of data regarding changes in total UPDRS in untreated patients to a two, three or four year point, generally following introduction of symptomatic therapy. Published sources include the CALM-PD study [57] and the Swedish selegiline study [58]. Unpublished data are also available from a long-term follow-up of patients originally enrolled in the PRECEPT study [59]. All these studies support a standard deviation of 12.0 units for the change in 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. Of course this change is deceiving, as the change would like-

ly 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 around 16 points, a value broadly consistent with the rate of change in total UPDRS in subjects prior to treatment. We have chosen to power our study to detect a four point effect, representing an overall 25% reduction in the rate of progression. We believe that a difference of this magnitude would be sufficient to influence clinical practice and may suggest the likelihood of longer term benefit.

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 subjects per group or a total 336 subjects.

8.4 Data Monitoring

An NINDS-appointed Data and Safety Monitoring Board (DSMB) will be established to monitor this clinical trial. The DSMB will be responsible for periodic review of the data related to adverse events throughout the trial. The frequency and format of the DSMB meetings, reports, will be established prior to study subject enrollment. The DSMB will meet approximately every 6 months.

8.5 Further Considerations in Data Analyses

Baseline Comparisons - Baseline values of relevant clinical and demographic variables will be tabulated by treatment group and by site.

Missing Data – If a subject is missing five or fewer items on the UPDRS at one visit, the values recorded on the previous visit will be carried forward. If more than five items are missing, all the data from the previous visit will be carried forward.

Outliers – This data will be visually checked and with scatter and residual plots. If certain outliers appear to be implausible, the sensitivity of the primary analysis to these outliers will be assessed by reanalyzing the data with the outliers removed.

Non-Compliance – Compliance, as measured by pill-count, will be summarized descriptively by treatment group and visit. The primary analysis will include all subjects according to the intent-to-treat (ITT) principle. If it is detected that a subject is not taking the study drug correctly, the sensitivity of the primary analysis to these subjects will be assessed by reanalyzing the data after removal of these subjects.

Premature Withdrawal or Lost to Follow-Up – Since subjects will continue in the study even after initiating symptomatic treatment we expect that premature withdrawals will be fairly low, estimated at 15% over the course of the study. To assess the possible influence of incomplete follow-up on the primary analysis, supportive analyses will be conducted with the 36 month outcome for these subjects imputed according to their UPDRS and symptomatic treatment history at the time they terminate. We will also conduct "best

case" and "worst case" analyses for these subjects to assess the sensitivity of our analyses to the "missing at random" assumption regarding dropouts.

9 DATA COLLECTION, SITE MONITORING, AND ADVERSE EVENT REPORTING

9.1 Records Keeping

9.1.1 Study File and Site Documents

The Investigator should have the following study documents accessible to the Monitor during the study.

1. FDA Form 1572
2. *Curriculum vitae* for Investigator and staff with delegated responsibility for direct subject evaluation
3. The signed IRB/REB form/letter stating IRB/REB approval of protocol, consent forms, and advertisement notices, documentation of the IRB/REB composition, and all IRB/REB correspondence including notification/approval of protocol amendments, notification of serious adverse events to the IRB/REB, and IRB/REB notification of study termination
4. IRB Membership Inquiry Form
5. IRB/REB approved consent form (sample) and advertisement
6. Signed protocol (and amendments, where applicable)
7. Signed Investigator Agreement forms
8. Signed subject consent forms
9. Copies of the completed eCRF worksheets (source), supplemental source notes and subject completed assessments
10. Authorization log (Delegation Log - Study Staff and Staff Related Duties) with names, signatures, initials and functional role of all persons completing protocol assessments, providing back-up to the site Investigator and Coordinator, if applicable, as well as staff entering data to the eClinical system
11. Copies of laboratory reports/printouts
12. Any source data/records not kept with the subject's hospital/medical records
13. Drug Dispensing/Return Log
14. Laboratory accreditation and relevant laboratory reference ranges
15. Signed and dated receipt of supplies
16. Record of all monitoring visits made by CTCC personnel
17. Copies of correspondence to and from Northwestern University and CTCC
18. Package Insert for Isradipine IR.
19. Certificate for Human Subject Protection Program (HSPP) for each individual named on the Delegation log who have direct subject contact
20. Copy of professional licensure/registration, as applicable, for each individual named on the Delegation Log, who has direct subject contact ensuring licensure is in the state in which the study will be conducted
21. Any other documentation as required by the CTCC (e.g., Conflict-of-Interest/Financial Disclosure)

22. Canadian Regulatory Forms (Canadian sites only)
23. General Correspondence

The Investigator must also retain all printouts/reports of tests/procedures, as specified in the protocol, for each subject. This documentation, together with the subject's hospital/medical records, is the subject's SOURCE DATA for the study.

9.1.2 Maintenance and Retention of Records

It is the responsibility of the site Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. Investigators will be instructed to retain all study records required by the CTCC and the federal regulations in a secure and safe facility with limited access for one of the following time periods based on notification from the CTCC.

Regulations require retention for:

- A period of at least two years after notification from the PI that a U.S. NDA (New Drug Application) has been approved for the indication that was investigated.
- Or if no NDA is filed or approved for such indication, a period of at least two years after the investigation is completed or discontinued.

The Investigator will be instructed to consult with the CTCC before disposal of any study records and to notify the CTCC of any change in the location, disposition, or custody of the study files.

Electronic Records:
An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study. At the conclusion of the study, a PDF (portable document format) file depicting the eCRFs for each site will be provided on electronic media for record keeping. In the event of an audit or regulatory authority inspection, the eCRFs can be printed out.

9.2 Role of Data Management

9.2.1 Data Management

An Internet accessible Electronic Data Capture (EDC) system for data management will be utilized for this study. This system is protected by 128-bit server certificates and utilizes authenticated, password-protected accounts for each site. The EDC system is designed to ensure timeliness and accuracy of data as well as the prompt reporting of data from the study on an ongoing basis to the study Principal and Co-Investigators. The system is compliant with relevant FDA regulatory requirements per 21 CFR Part 11.

The University of Rochester's Biostatistics Center will be responsible for design of the randomization scheme, creation of analytical databases, and the statistical analysis plan.

Data management staff at the CTCC will be responsible for all data collection procedures.

Data review, coding and query processing will be done through interaction with the CTCC, site personnel and the Study Monitor. Queries will be generated in real-time as the data is entered. Once the data are submitted to the EDC system, it is immediately stored in the central study database located at the CTCC and are accessible for review by data management staff. Any changes to the data will be fully captured in an electronic audit trail. As data recorded by sites in eCRFs are received, narrative text of adverse events and concomitant medications will be periodically coded using established coding mechanisms.

The cycle of electronic data entry, review, query identification/resolution, and correction occurs over the course of the study period until all subjects have completed the study.

Data will be securely transferred to the Biostatistics Center. Once the Biostatistics Center and the CTCC, in conjunction with the Principal Investigator, agree that all queries have been adequately resolved and the database has been deemed "clean", the database will be officially signed off and deemed locked. All permissions to make changes (append, delete, modify or update) the database are removed at this time.

All site personnel, Northwestern University staff and CTCC staff will remain blinded as to treatment assignments until the conclusion of the entire study. The treatment assignments are not part of the CTCC electronic database. A designated unblinded programmer and unblinded statistician in the Biostatistics Center will have access to the treatment assignments, and these individuals will not communicate about study-related matters to any other staff involved in the study. The study code will be broken by the study-responsible statistician after all outstanding substantive data queries have been resolved.

9.2.2 Investigator Site

This study will be conducted under the supervision and direction of the site Investigator(s) designated by the STEADY-PD III Steering Committee as the site Principal Investigator at the address provided to the CTCC.

Clinical supplies will be sent to the address specified to the CTCC by the Investigator.

The Investigator must not conduct the study at any sites other than the one(s) designated by the STEADY-PD III Steering Committee.

The protocol, informed consent form, and advertisement notices will be approved by the site's specified institutional IRB/REB.

Each site Investigator is responsible for providing copies of the protocol and all other information relating to the preclinical and prior clinical experience, which were furnished to him/her, to all physicians and other study personnel responsible to them who participate in

this study. The site Investigator will discuss this information with them to assure that they are adequately informed regarding the study drug and conduct of the study. The site Investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities.

9.2.3 Study Monitoring

CTCC Monitoring Staff

CTCC personnel with primary responsibility for this study are the assigned CTCC Clinical Monitor and Project Managers. If either the CTCC Clinical Monitor or Project Manager changes, the CTCC will inform Northwestern University and the investigative team in writing.

All aspects of the study will be monitored by authorized individuals in compliance with Good Clinical Practice (GCP) and applicable regulations. The Monitors will review, on a regular basis, the progress of the study with the Investigator and other site personnel.

9.2.4 Study Committees

9.2.4.1 Steering Committee

The Steering Committee (SC) is composed of the Principal and Co-Principal Investigators, Biostatistician, CTCC Clinical Monitor, NINDS Project Scientist, and independent investigator members of the Parkinson Study Group with expertise in Parkinson disease. The SC is responsible, along with the Northwestern University, for the design of the study protocol and analysis plan, and oversees the clinical trial from conception to analysis and publication.

9.2.4.2 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be appointed that will be responsible for periodic review of the data related to adverse events throughout the trial. The frequency and format of the DSMB meetings, reports, will be established prior to study subject enrollment.

9.2.5 Case Report Forms

Sites will enter subject information and data into an electronic case report form (eCRF) in the Electronic Data Capture (EDC) application. The eCRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore the eCRFs must be completed for each subject screened or enrolled according to the subject's source data on a per-visit basis. Authorized study personnel will each be granted access to the electronic data capture tool via provision of a unique password-protected user-ID that will limit access to enter and view data specifically for subjects enrolled at their site. ***Data should be entered into the EDC system within 5 business days of a subject's visit.***

Sites will be supplied with a set of source document worksheets that correspond to the electronic case report form (eCRF). The worksheets will serve as source documents and are required to be used to enter data into the eCRFs. Sites will initially enter all data into the subject's medical chart and/or onto source documentation worksheets prior to entering data into the eCRFs via computer stations connected remotely to the central server through an Internet browser.

9.2.6 Electronic Signatures

An electronic signature from the site Investigator is required on the following eCRFs:

- Investigator Signature Form (for each visit)
- Adverse Event Form (at the conclusion of the study)
- Adverse Event Follow up Log (not required if AE log is blank)

It is the site Investigator's responsibility to ensure that entries are proper and complete. During entry of data, error checks will be performed by the EDC that will immediately flag problematic data (i.e., missing, out of range, inconsistent) allowing for sites to correct the data at that time. Error checks will be implemented in the EDC based upon specifications defined in the data management plan.

The data entered from the eCRFs will be securely transmitted to a central database stored on a secure server located at the CTCC. Upon completion of a subject's visit or the study, sites have the option to print the completed eCRFs depicting the data that were entered.

At the conclusion of the study, the site will be provided with a PDF (portable document format) file on electronic media depicting eCRFs for their site. The PDF file should be printed for each subject participating in the study and filed in the subject's binder.

9.2.7 Monitoring Visits

To ensure compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements, the monitor or representative is responsible for monitoring that sites conduct the study according to the protocol, standard operating procedures, and other written instructions and regulatory guidelines.

Monitoring visits by a Study Monitor will be arranged in advance, at a mutually-acceptable time, with site personnel. The site personnel must allow sufficient time for the Study Monitor to review CRFs and relevant source documents and queries. The Study Coordinator and/or Investigator(s) should be available to answer questions or resolve data clarifications.

9.2.8 Primary Source Documents

The Investigator must maintain primary source documents supporting significant data for each subject in the subject's medical notes. These documents, which are considered 'source data', should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the subject is being studied
- General information supporting the subject's consent to participate in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the Investigator(s), occurrence (or lack) of adverse events, and changes in medication usage including the date the study drug commenced and completed
- Any additional visits during the study
- Any relevant telephone conversations with the subject regarding the study or possible adverse events
- Original, signed informed consent forms for study participation

The Investigator must also retain all subject specific printouts/reports of tests/procedures performed as a requirement of the study (e.g., laboratory and ECG reports). Laboratory reports from the central laboratory will be signed and dated by the Investigator following review and filed with the subject's source documents. This documentation, together with the subject's hospital/site medical records, is the subject's 'source data' for the study. During monitoring visits the Study Monitor will need to validate data in the eCRFs against these source data.

9.2.9 CRF Worksheets

Sites will be supplied with a set of worksheets that correspond to the electronic case report form (eCRF) for this study. The worksheets will serve as source documents for study observations and assessments and should be used to enter data into the eCRF. Additional source documentation for information not specifically included on the source document may be recorded on a separate document.

9.2.10 Closeout Visit

Following the completion of the study, Study Monitor(s) or designee may conduct an on-site closeout visit or a telephone closeout visit to ensure that all data queries have been resolved, any protocol deviations are documented appropriately, all relevant study data have been retrieved, that study drug and clinical supplies have been/will be properly returned and that the Investigator has copies of all study-related data/information on file and archive responsibilities have been reviewed.

9.3 Quality Assurance

9.3.1 QA Audits/Site Visits

During the course of the study and after it has been completed it is likely that one or more study site visits will be undertaken by authorized representatives of the CTCC.

The purpose of the audit is to determine whether or not the study is being, or has been, conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a subsequent regulatory authority inspection.

If such audits are to occur, they will be arranged for a reasonable and agreed time. Site staff will receive feedback after these visits have taken place. Action items noted in this correspondence should be attended to within 1 week of receipt of the correspondence.

9.3.2 Regulatory Inspections

The study may be inspected by regulatory agencies, such as the Food and Drug Administration (FDA). These inspections may take place at any time during or after the study and are based on the local regulations as well as ICH guidelines.

9.4 Adverse Event Reporting

9.4.1 Adverse Event (AE) Definition

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to study drug.

Some examples of adverse events are:

- A change, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition.
- A deterioration in the subject's condition due to the subject's primary disease or a pre-existing condition.
- Development of an intercurrent illness during the study.
- Development of symptoms which may or may not be related to the use of a concomitant medication or study drug.
- Appearance of abnormal laboratory results or significant shifts from baseline, but still within the reference ranges, following treatment with the study drug, which the Investigator considers clinically important.

9.4.2 Serious Adverse Events (SAE)

A serious adverse drug event is defined as any adverse event that occurs at any dose that results in any of the following outcomes:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant disability/incapacity; or
- a congenital anomaly/birth defect.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include (but are not limited to) allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

This category also includes any event the site Investigator or the CTCC Clinical Monitor judges to be serious or which would suggest a significant hazard, contraindication, side effect or precaution. It can also involve the withdrawal of a subject from a study due to abnormal lab values, excluding screening labs.

Continued monitoring of marketed products for adverse events is essential and depends on voluntary reporting of adverse events. For purposes of this study the following experiences/events will be considered Serious Adverse Events and reportable to the FDA and Health Canada:

1) Death
2) Life threatening adverse event
3) An event that is Serious AND Unexpected

Reports of serious adverse events, as defined above, require immediate notification (within 24 hours of the site's awareness) to the CTCC Project Manager or CTCC Clinical Monitor whether or not the Investigator believes that the experience is related to study drug or expected.

All other types of serious adverse events will be recorded on the study Adverse Event Log and reported to the site's respective IRB/REB per the institution's reporting requirements.

Note: Hospitalizations that fulfill one of the following conditions do not have to be reported as an SAE:

- Those for elective surgical interventions for which the date had already been determined/planned before the study participation
- Those for situations where no untoward medical occurrence has occurred (e.g. hospitalization for cosmetic surgery)

9.4.3 Recording of Adverse Events

At each subject visit the site study staff will assess adverse events by recording all voluntary complaints of the subject and by assessment of clinical and laboratory features. At each study visit, the subject should be questioned directly regarding the occurrence of any adverse event since his/her last visit.

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, should be recorded on the CRF Adverse Event Log. This will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, contributing factors, and any action taken with respect to the study drug.

This recording of adverse events will commence with the signing of the informed consent and continue until 2 weeks after stopping study drug at Visit 11 (Visit 10 +2 weeks) or Premature Withdrawal Follow-up visit. All experiences/events occurring up to the Baseline visit will be recorded as Medical History unless possibly related to a study procedure or the severity increases.

New Serious Adverse Events (SAEs) and unresolved AEs ongoing at the time of the last subject visit Visit 11 (Visit 10 +2 weeks) on the AE CRF page must be followed for 30 days from last visit or until resolution, whichever occurs first. A follow-up phone call will be made to all subjects who have unresolved AEs or SAEs 30 days from the date of the final study visit (Visit 11 or Premature Withdrawal Follow-up visit).

FOR ADVERSE EVENTS: The Adverse Event Log CRF must be completed and be signed by the Investigator. This will include information on any action taken as a result of the adverse event and the Investigator's opinion of the possible relationship between the experience and the study drug or participation in the study.

All subjects with unresolved adverse events or SAEs at the time of their final study visit (Visit 11 or Premature Withdrawal Follow up Visit) should have a phone call approximately 30 days after their final visit. The purpose of this phone call is to assess the final outcome of the unresolved adverse events as either resolved or ongoing. The Adverse Event Follow-Up Log CRF will be used to document this follow-up and will be signed by the Investigator.

FOR PROTOCOL DESIGNATED SERIOUS ADVERSE EVENTS (death, life threatening event, event that is serious AND unexpected: The Investigator or their designee must

fill out the MedWatch FDA 3500 form for serious adverse event (SAE). This will include: an identification that serious experience criteria have been met; a detailed description of the experience and other relevant information; the current status of the experience; if the subject has died, the date of death and autopsy report, if available; and the Investigator's current opinion of the relationship between the experience and the study drug/participation in the study. The electronic MedWatch form should be sent to the Project Manager for review and editing.

9.4.4 Adverse Events Causality Definitions

For each adverse event, the relationship to the study drug must be recorded as one of the following on the Adverse Event Log:

TERM	DEFINITION	CLARIFICATION
Unrelated	No possible relationship	The temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible.
Unlikely	Not reasonably related, although a causal relationship cannot be ruled out	While the temporal relationship between drug exposure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug.
Possibly	Causal relationship is uncertain	The temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown, de-challenge or re-challenge information is either unknown or equivocal, and while other potential causes may not exist, a causal relationship to the study drug does not appear probable.
Probably	High degree of certainty for causal relationship	The temporal relationship between drug exposure and the adverse event onset/course is reasonable. There is a clinically compatible response to de-challenge (re-challenge is not required), and other causes have been eliminated or are unlikely.
Definite	Causal relationship is certain	The temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated, and the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.

9.4.5 Adverse Event Severity Definitions

The severity of each adverse event must be recorded as one of the following on the Adverse Event Lo5g:

MILD	No limitation of usual activities
MODERATE	Some limitation of usual activities
SEVERE	Inability to carry out usual activities

9.4.6 Responsibilities of Investigator/CTCC for Reporting Serious Adverse Events

- The Investigator should record all serious adverse events that occur during the study period on the Adverse Event Log and in the appropriate source documents.
- Study Period: For the purposes of reporting serious adverse events, the study period is defined as the time period from when the subject signs the informed consent through Visit 11 (Visit 10 +2 weeks) or Premature Withdrawal Follow-up visit.
- The Investigator should notify the CTCC Project Manager (PM) by telephone within 24 hours of his/her becoming aware of the occurrence of the protocol defined serious adverse event. The PM will in turn notify the CTCC Clinical Monitor and Independent Medical Monitor. The Study Coordinator will fill out the MedWatch form provided by the CTCC, and email or fax it to the CTCC Project Manager (preferably prior to calling the CTCC). The MedWatch form must be completed for the protocol specified Serious Adverse Events (death, life threatening event, any event that is serious and unexpected).
- Upon completion of the telephone report, the CTCC Project Manager will enter the appropriate subject information into the Incident Module. Upon completion of entry of the incident, an immediate notification will be disseminated by email to the Steering Committee (including PIs and Co-PI), CTCC Clinical Monitor, Independent Medical Monitor, Field Monitoring Staff, CTCC Project Staff, and Biostatistics Center Staff.
- The following information should be supplied if available at the time of the telephone call: study number, site number, subject number, whether the test treatment has been discontinued, date of onset of event, event description, whether event required treatment, death and autopsy report, an identification of which criteria for a serious experience have been met, the Investigator's current opinion of the relationship between the event and the study drug or study participation.
- The Investigator will comply with his/her local Institutional Review Board/Research Ethics Board regulations regarding the reporting of adverse events

9.4.7 Reportable Experiences/Events

The following incidents will be considered reportable events and will be reported to the CTCC within 24 hours of the event, or the site Investigator's knowledge of the event.

- Temporary suspension of Study Drug
- Study Drug Discontinuation

- Study Drug reduction/re-challenge
- Subject withdrawal
- Pregnancy
- Protocol specified Serious adverse event (SAE) (death, life threatening event, any event that is serious and unexpected)
- Emergency treatment disclosure
- Overdosage
- Initiation of symptomatic therapy
- Completion of DaT Scan

9.4.8 Follow-Up of Unresolved Experiences/Events

- All serious adverse event information will be followed for 30 days from last study visit or until resolution, whichever occurs first.
- The site Investigator and CTCC Clinical Monitor will, as appropriate, provide further information on the event especially if the event has not resolved or stabilized at the time of completion of the MedWatch form. This may involve contacting other clinicians responsible for the subject's care to obtain information on diagnoses, investigations performed and treatment given.

All serious adverse events occurring between the institution of protocol specific procedures (i.e., when the subject signs the informed consent) through Visit 11 (Visit 10 +2 weeks) or Premature Withdrawal Follow-up visit must be recorded and reported; then followed by the site Investigator for 30 days from the last study visit or until resolution as noted above.

10 HUMAN SUBJECTS

10.1 Compliance Statement

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines promulgated by the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA), and any applicable national and local regulations including FDA regulations under 21 CFR Parts 11, 50, 54, 56, 312 and 314.

All procedures not described in this protocol will be performed according to the study Operations Manual unless otherwise stated. Laboratory tests/evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the central laboratory manual unless otherwise stated.

10.2 Informed Consent

This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50. The CTCC must be given an opportunity to review the consent form prior to site IRB/REB submission and before it is used in the study.

In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, together with any potential hazards/risks must be read and/or explained to each subject. Each subject will sign such an informed consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

During the consent process, subjects will also be asked for permission to be contacted by the study principal investigators or their representatives for future long term follow up after study completion. Subjects who consent to be contacted for future research will be

asked to provide their preferred contact information (phone, mail, email, or other preferred contact method.). This information will be stored in a secure, password protected database at the University of Rochester for 20 years. This will allow centralized follow up for current and former subjects in this study, using methods convenient to the subjects (e.g., regular mail, telephone or internet contacts). All potential research projects wishing to use subjects who have agreed to future research must be reviewed and approved by the STEADY-PD III steering committee. Any future research involving these subjects will require a separate IRB approved protocol and consent process. This will allow us to 1) minimize subjects lost-to-follow-up 2) allow for contact and consent of subjects for the systematic collection of data following completion of the parent study and 3) simplify communications with current and former subjects about future research opportunities through direct communication with subjects without having to go through individual sites.

A copy of the consent form will be given to the subject, or legal guardian, and this fact will be documented in the subject's record. The subject must be assured of the freedom to withdraw from participation in the study at any time.

It is the Investigator's responsibility to make sure that the subject understands what she/he is agreeing to and that written informed consent is obtained before the subject is involved in any protocol-defined procedures including screening procedures. It is also the Investigator's responsibility to retain the original signed consent form and provide each subject with a copy of the signed consent form.

10.3 Institutional Review Board/Independent Ethics Committee

Northwestern University and the CTCC will supply all necessary information to the Site Investigator for submission of the protocol and consent form to the IRB/REB for review and approval. The Site Investigator agrees to provide the IRB/REB all appropriate material. The trial will not begin until the site Investigator has obtained appropriate IRB/REB approval. A copy of the approval letter and approved consent form must be submitted to the CTCC.

The Investigator will request from the IRB/REB a composition of the IRB/REB members reviewing the protocol and informed consent. Appropriate reports on the progress of this study by the Investigator will be made to the IRB/REB and the CTCC in accordance with institutional and government regulations. The CTCC will notify the site when the IRB/REB may be notified of study completion. It is the Investigator's responsibility to notify the IRB/REB when the study ends. This includes study discontinuation, whether it is permanent or temporary. A copy of the site IRB/REB's acknowledgement of study completion must be submitted to the CTCC.

The Investigator will discuss any proposed protocol changes with the CTCC Project Manager and no modifications will be made without prior written approval by CTCC and Northwestern University, except where clinical judgment requires an immediate change

for reasons of subject welfare. The IRB/REB will be informed of any amendments to the protocol or consent form, and approval, where and when appropriate, will be obtained before implementation.

10.4 Protocol Amendments

Changes to the protocol will only be made via an approved protocol amendment. Protocol amendments must be approved by the PI, the study's Steering Committee and each respective site's IRB/REB prior to implementation, except when necessary to eliminate hazards and/or to protect the safety, rights or welfare of subjects.

10.5 Subject Confidentiality

Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB/REB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor's designee.

The site Investigator must assure that the privacy of subjects, including their personal identity and personal medical information, will be maintained at all times. U.S. sites have additional privacy obligations to study subjects under the Health Insurance Portability and Accountability Act (HIPAA). Subjects will be identified by code numbers on case report forms and other documents submitted to the CTCC.

After a subject signs an informed consent, it is required that the site Investigator permit the study monitor, independent auditor or regulatory agency personnel to review the signed informed consent(s) and that portion of the subject's medical record that is directly related to the study including electronic medical records. This shall include all study relevant documentation including subject medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the subject is in the study, and autopsy reports for deaths occurring during the study (when available).

The subject's Authorization allows the CTCC to receive and review the subjects' protected health information that may be re-disclosed to any authorized representative of the PI, CTCC or central laboratory facility for review of subject medical records in the context of the study.

10.6 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB/REB, the NINDS, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

11 DATA SHARING

Government funded studies require data sharing. All subjects will be informed that their de-identified data collected will be made available for sharing. The study data collected will be coded and may be used for future unspecified research purposes, for example to develop future studies of PD and related disorders.

The research information collected will be labeled with a unique identification code. By using this code, the subject's identity will not be disclosed to any researchers using this data in the future.

12 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Parkinson Study Group. Any presentation, abstract, or manuscript on the primary results will be made available for review by the NINDS and the DSMB prior to submission.

13. REFERENCES

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