STEADY-PD III
(Efficacy Assessment of Isradipine in early Parkinson Disease)

STATISTICAL ANALYSIS PLAN AND POWER CALCULATIONS

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1. Introduction

A. The statistical analysis of the STEADY-PD III study will be performed by the Statistical Center located in the Department of Biostatistics and Computational Biology (DBCB) in the University of Rochester Medical Center, under the direction of the primary biostatistician, Dr. David Oakes.

B. Following our standard procedures, Dr. Oakes will remain blinded throughout the study in order that he may participate fully in Steering Committee deliberations. Dr. Oakes will attend open sessions of the DSMB but not closed sessions, in which data by treatment arm may be discussed. Tabulations of data by coded treatment group and interim analyses as described in Section 8 of this document will be performed by, or under the direction of, the unblinded biostatistician, Dr. Michael P. McDermott. Dr. McDermott will attend the closed sessions of the DSMB.

C. The detailed statistical analysis plan will be finalized during the course of the study, implemented in SAS (version 9.2 or higher) and, prior to unblinding, tested on a preliminary version of the STEADY-PD III database, using an artificially simulated "treatment" classification. The main features of this plan are given below. On completion of the final analysis the DBCB will produce full analysis notebooks for distribution to Drs. Simuni and Biglan, to the Steering Committee and to the DSMB. Searchable CDs containing the same information will also be prepared. The DBCB will assist in preparation of abstracts, power point presentations and manuscripts from the study.

2. General Considerations

A. *Intent-to-Treat.* Efficacy analyses will use the intent-to-treat principle, whereby all subjects are kept in their assigned treatment groups for statistical analysis, even if they discontinue study medication or continue on a reduced dosage. Subjects who discontinue study medication will be encouraged to remain in the study and their data will be used in the primary efficacy analysis. Subjects who have no post-baseline efficacy data will be excluded from the primary analysis as their primary outcome variable will be missing. The primary analysis will compare the active treatment group (all subjects randomized to receive active isradipine) to the placebo group. All P-values for efficacy outcomes will be two-sided.

B. *Baseline Characteristics.* Demographic and clinical characteristics, including age, gender, race and ethnicity, years of education, time since PD diagnosis, UPDRS score at entry including its mental, motor and ADL components, MDS-UPDRS, Modified Rankin Score, Modified Hoehn and Yahr score, PDQ-39 score, MOCA score (adjusted for education level) of the two treatment groups will be presented. Systolic and Diastolic blood pressure and other vital signs data will also be shown.

C. *Subject Disposition.* Losses to follow-up, compliance to study medication, protocol violations and other notifiable incidents will be tabulated. A CONSORT type diagram showing the progress of all enrolled subjects through the study will be prepared.

(Numbers of subjects screened but ineligible, and those eligible but not enrolled, will be provided by the CTCC).

3. Primary Efficacy Analysis

A. Outcome Variable. The pre-specified primary outcome variable will be the change from baseline to the three-year follow-up visit in the total score from Parts I, II and III of the UPDRS score (mental, motor and ADL components). We anticipate that by the three year visit a substantial majority of participants will be receiving symptomatic medication. Unlike in previous studies in early PD (e.g. DATATOP, PRECEPT, QE3)[1-3] subjects who require symptomatic treatment (typically levodopa or dopamine agonists) during the course of the study will continue in the study, receiving their assigned study medication. By this strategy we hope to minimize drop-outs. For subjects receiving symptomatic medication the UPDRS will be assessed in the ON state, based on the subject/ investigator defined BEST ON, approximately 1 hour after dose of symptomatic therapy). Subjects who do not complete the three-year visit will have their primary outcome variable set to missing: a variety of sensitivity analyses (see below) will be conducted to assess the influence of these subjects on the primary analysis.

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

C. Adjustments to the Analysis. (i) It may occasionally happen that certain items on the UPDRS are missing at a particular visit, for example if a subject is unable to perform a test due to injury. To enable the valid data from that visit for that subject to be used in the analysis, single missing items on the UPDRS will be carried forward from the subject's previous visit. A maximum of five missing items may be carried forward in this way, including from the baseline visit to the one-month visit if necessary. Items missing at baseline may be carried forward from the screening visit. (ii) For analyses that include the enrolling site as a stratification factor, sites that enroll fewer than four subjects will be combined to form a single "super-site".

4. Secondary Efficacy Analyses

A. 36-month data. The changes from baseline to 36 months in the following measures of disability will be analyzed in a similar fashion as that for the primary outcome variable

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. Proportion of subjects receiving symptomatic therapy
e. Current usage of symptomatic therapy utilization as measured by levodopa equivalence dose[4]
f. Prevalence of motor complications as measured by UPDRS IV subscale (complications of therapy) for those subjects that have initiated symptomatic therapy

II. Cognitive disability
a. The change in the cognitive function as measured by the change in the MoCA [5, 6]

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 Non-motor and Motor Experiences of Daily Living scores of the MDS-UPDRS (Part I and II)
c. The change in the modified Schwab and England scale
d. The change in Parkinson Disease Quality of Life Questionnaire-39 (PDQ-39) [7]

B. Longitudinal Analyses. Outcome data from all subject visits will be plotted over time by treatment group.

I. Time-dependent events

Kaplan-Meier plots and Cox regression will be used to analyze the following events:
a. Time to initiation of symptomatic therapy
b. Time to complications of symptomatic therapy, including wearing-off, dyskinesias and sudden "on-offs".

II. Early Effects:
a. Plots of the mean and standard error of the total UPDRS and related outcome variables will be constructed.
b. Changes in total UPDRS from baseline to the one year visit or to the initiation of symptomatic therapy between treatment groups will be compared using analysis of covariance (as for the three-year analysis).
c. Changes in total UPDRS following the introduction of symptomatic therapy will be compared between treatment groups in the same way.
d. Multiple regression analysis and other techniques as appropriate will be used to examine whether early outcomes (e.g. short-term changes in UPDRS, time to initiation of symptomatic therapy) are useful predictors of long-term disability.

C. Sensitivity Analyses. A variety of sensitivity analyses will be conducted to assess the robustness of the comparison between treatment groups.

I. Non-parametric methods. Residual plots will be examined. In the event that these show outliers or pronounced non-normality, supplementary analyses will be performed after deletion of outliers and/or using appropriate non-parametric methods.

II. Missing Data. Effects of missing data will be assessed (i) by multiple imputation and (ii) by "best case" and "worst-case" analysis and (iii) by the use of mixed models (which use intermediate study data to project final study outcomes when these are missing).

III. Influence of Symptomatic Medication. Supplementary analyses of the final study outcomes will be conducted with current use of symptomatic medication (levodopa equivalents) added as an additional predictor variable. The purpose of this analysis is to assess whether any differences seen in the primary outcome variable could be attributed to differential use of symptomatic therapy between the treatment groups.

D. Subgroup Analyses – Including Gender and Race/ Ethnicity

Recognizing that the study will not have high power to detect treatment effects among subgroups, we will conduct exploratory analyses to check the consistency of treatment effects on the primary and secondary efficacy measures in relation to selected baseline characteristics, including gender and race/ ethnicity. The analysis will use two approaches (i) repeating the primary analysis for each subgroup (for example men and women; minority and non-minority) separately, (ii) inclusion of additional terms in the analysis of covariance model to represent the overall effect of the characteristic (do men progress faster than women?) and for the interaction of the treatment with the characteristic (does the effect of the treatment differ between men and women?). Results for each race/ethnic grouping will be tabulated separately.

5. Safety and Tolerability Analysis

A. Primary Safety and Tolerability Outcomes.

I. The ability to complete the 36 months study on the originally assigned treatment dosage
II. The proportion of subjects requiring dosage reductions secondary to intolerability
III. The frequency of adverse events and serious adverse events
IV. Laboratory and EKG abnormalities
V. An interim tolerability analysis will be performed after the first 60 subjects complete titration period of the study (Visit 03) as discussed in section 8.C.

B. *Procedure.*

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 medication. 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 medication. 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 supine 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 by Fisher's exact tests

C. Analysis by Subgroups, Including Race and Gender.

Primary safety and tolerability data will be tabulated separately for selected subgroups of the population defined by baseline characteristics, including gender and race/ethnicity.

6. Exploratory Analysis

An analysis of the correlation between clinical efficacy measures and serum 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.

7. Power and Sample Size Considerations

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 [8] and the Swedish selegiline study [9]. Unpublished data are also available from a long-

term follow-up of patients originally enrolled in the PRECEPT study [2]. 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 likely be much greater in the absence of symptomatic treatment. If we assume that treatment with levodopa or a dopaminergic agonist provides a "bonus" of 12 points, then the underlying true decline in function over this period would be 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 underlying 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.

The Table below shows the effect of higher than expected withdrawal rates (20% and 25%) expressed in three alternative metrics (A) The power to detect a 4.0 point difference, (B) The effect size that would be detectable with 80% power and (C) the number of additional subjects that would need to be enrolled to maintain power at 80% to detect a 4.0 point difference.

Overall Withdrawal Rate	Power (A)	Effect Size (B)	Additional Subjects (C)
15%	80%	4.0 pts.	0
20%	78%	4.1 pts	21
25%	75%	4.25 pts.	45

Power for key secondary outcomes

We will also examine power for some key secondary outcomes of this study.
Time to Initiation of Symptomatic Therapy. After allowing for 15% dropouts, half of these prior to need for symptomatic therapy, and 10% of subjects not requiring symptomatic treatment three years after enrollment, we estimate that approximately 275 subjects will have reached this milestone by the conclusion of the study. By the formula of George and Desu[10], this translates to a detectable hazard ratio of 0.71, i.e. a 29% reduction in the risk of reaching this milestone per unit of time.

Rationale for the selection of this secondary outcome:
Time to initiation of symptomatic therapy has been a primary outcome in a number of previously completed studies that examined the efficacy of putative disease modifying interventions[2, 3, 11]. While it has been criticized for the subjective nature of the measure and being impacted by the change in the treatment algorithms that overall lead to the earlier initiation of symptomatic therapy, nevertheless it can be considered a surrogate measure of the disease progression and as such should be considered as a key secondary outcome.

Complications of Therapy. In the CALM-PD study approximately 40% of subjects enrolled experienced complications of therapy within two years of follow-up. Since subjects in CALM-PD were enrolled at the time they needed therapy, the experience of our subjects after three years of follow-up is expected to be similar. A total of 120 subjects reaching this milestone gives a detectable hazard ratio of 0.60, i.e., a reduction of 40% in the risk per unit of time. For the purpose of this analysis complications of therapy will be measured by UPDRS IV subscale (complications of therapy) for those subjects that have initiated symptomatic therapy

Rationale for the selection of this secondary outcome:
Time to onset of motor complications is considered an important milestone in the disease progression signifying transition from early to more advanced disease and has been used as a primary outcome in a number of previously completed studies[12-14] . A disease modifying intervention that shows an impact on this milestone will have a meaningful impact on the progression of disability and as such should be considered as a key secondary outcome.

Symptomatic Therapy (Levodopa Equivalent Dosage). Data on 168 subjects who had a follow-up visit in the "Postcept" extension of the "Precept" study between 2.5 and 3.5 years after their enrollment in Precept showed a mean dosage of 390 units and s.d. of 277. These numbers give a detectable effect size of 92 units, approximately a 25% reduction in the dosage of symptomatic therapy.

Rationale for the selection of this secondary outcome:
The dose and type of symptomatic therapy are influenced by a large number of variables but nevertheless generally can be considered a surrogate measure of the disease severity. In addition there is consistent data on correlation of the dose of levodopa with the time to onset of motor complications[14]. A disease modifying intervention that shows an impact on this milestone will have a meaningful impact on the progression of disability and as such should be considered as a key secondary outcome.

MDS-UPDRS. Data on the 67 subjects from the PPMI cohort who have been followed for three years from enrollment, gives changes (mean, s.d.) in the non-motor EDL of (2.55, 4.37) and in the motor EDL of (3.07, 5.16). These translate to detectable effect sizes of 1.5 points on the non-motor EDL scale and 1.7 points on the motor EDL scale.

Rationale for the selection of this secondary outcome:
Patient reported outcomes are an important measure of efficacy of any intervention. Non-motor disability is an intrinsic part of overall PD disease burden, is directly linked to the spread of PD pathology and has been shown in multiple studies to correlate with the disease related quality of life impairment [15]. MDS-UPDRS has been substantially expanded compared to UPDRS to capture patient reported scope of non-motor disability. A disease modifying intervention that shows an impact on this milestone will have a meaningful impact on the progression of disability and as such should be considered as a key secondary outcome.

8. Interim Analyses

A. Procedure. Interim analyses will be planned by the primary biostatistician (Dr. Oakes) with input from the PI's and Steering Committee, but executed by the unblinded statistician (Dr. McDermott) and included in the closed session reports to the DSMB.

B. 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.

C. Interim analysis of the Pharmacokinetic (PK) data. An interim PK analysis will be performed 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 analyzed. Only data on the subjects who have reached 10mg dose of study drug (Isradipine IR or placebo) will be included in the interim analysis. For subjects receiving active isradipine, we expect 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, remediating actions will be implemented as described in the protocol.

Interim futility and efficacy analysis. Following a decision by NINDS based on a recommendation from the Data and Safety Monitoring Board at their October 11, 2017 meeting, the proposed interim and futility analysis will NOT be performed. The quoted text below, taken from the original SAP, is therefore inoperative. "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 will be terminated for futility if the interim analysis shows that the conditional power of rejecting the null hypothesis in favor of a beneficial effect of isradipine is lower than 20% under any scenario that is consistent with the data accrued at that time. A two-sided P-value in favor of isradipine of less than 0.001 will be required to stop for efficacy at the interim analysis. 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. 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."

E. General Reporting to the DSMB. Two weeks prior to each DSMB meeting the Biostatistics Center will distribute "open" and 'closed" session reports. The open session

report will include only aggregate data; the closed session report will include the same data classified by treatment group, coded Red or Blue. The actual codes - Active Isradipine or Placebo - will be available to the committee should the DSMB Chair request this information. In any case the color coding will be consistent within and between reports. The reports will include tables of subject enrollments, baseline characteristics, disposition, listings of deaths, withdrawals, unblindings, serious adverse events, drug discontinuations and dosage reductions and other study incidents. Adverse events, out of range laboratory values, major changes from baseline in vital signs data including blood pressure measurements, (see **5B** above) will be tabulated with flags indicating nominal imbalances between treatment groups ($P < 0.05$). Home blood pressure measurements will not included in the study data-base, however clinical monitor actions in response to blood pressure alerts will be included.

9. Sample Size Review and Re-estimation

The assumptions made in the power calculation will be kept under constant review. While primary outcome data will not be available for any subject till three years after commencement of enrollment, we will monitor recruitment and retention rates throughout and compare the aggregate experience of Steady-PD III subjects, including short-term changes in UPDRS, and the usage of symptomatic therapy, with those observed in other recent studies in early PD, including PRECEPT and QE3. Where applicable, for example in regards to dosage adjustments, we will also compare the aggregate experience in STEADY-PD III with the experience in STEADY-PD II. A formal reassessment of the required sample size, including a blinded evaluation of the variability of the primary outcome measure, will be made prior to the conclusion of enrollment in the study and at the time of each interim analysis.

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STEADY-PD III STATISTICAL ANALYSIS PLAN - CLARIFICATION

The purpose of this document is to clarify two aspects of the SAP from December 2017.

(1) *Combining sites with low enrollment*. The SAP, section 3.C. states that for analyses that use sites as a stratification factor, sites with enrolling fewer than four subjects will be combined to form a single "super-site". The sites affected are 016 (Ottawa) three subjects, 030 (Calgary) two subjects, 034 (IND) three subjects, 069 (PMDI), three subjects, 110 (UC Irvine), three subjects, 132 (LSU) three subjects, 139 (PHREI), two subjects, 305 (Alberta) three subjects, making a grand total of 22 subjects.

(2) *Influence of Symptomatic Medication on the Primary Outcome*. Section 4C. III states that "Supplementary analyses of the final study outcome will be conducted with current use of symptomatic medication (levodopa equivalents) added as an additional predictor variable''. Since use of symptomatic medication is a post-randomization variable and may be determined in part by post-randomization values of the outcome variable, it should not be used as a predictor variable. Subjects who show a more rapid early decline may be more likely to receive symptomatic medication. This could result in an artefactual positive correlation between use of symptomatic medication and rapidity of disease progression which might distort the estimate of the randomized treatment. To avoid this artefact we will estimate the effect on the primary outcome of both current and cumulative dosages of symptomatic medication from a mixed model analysis using data from all study visits and which explicitly allows subjects to have differing underlying rates of disease progression. In essence this analysis uses each subject as his or her own control in estimating the influence of symptomatic medication on disease progression. It will be performed on the aggregate data from the final study data-base, prior to breaking the blind as to the randomized treatment. The estimated coefficients of the two LED variables (current and cumulative levodopa equivalent doses) will then be used to adjust each subject's final UPDRS value to the projected value that the subject would have had if he or she had not received symptomatic medication. Since these projections will not use the randomized treatment, the treatment effect on the projected outcome variables can be estimated using the same model as the primary analysis, i.e. stratifying by site and including baseline UPDRS as a covariate. This analysis will have the correct alpha-level under the overall null hypothesis (no effect of isradipine relative to placebo on either disease progression or usage of symptomatic medication) irrespective of whether the relationship between these two outcome variables is modeled accurately. A member of the Steering Committee asked about the possible influence of body weight on the effect of LED. To assess this we conducted preliminary analyses on the aggregate study data with the raw values of current and cumulative LED divided by the subject's weight giving LED per kilo of body weight. In addition to confirming the reality of the artefact described above the results were very similar to those using the original values of LED, so we propose not to adjust for body weight in this prespecified supplementary analysis.

David Oakes (12/28/2018)

Statistical Analysis Plan Version Date	Summary of Changes
1-Sep-14	Original Version
6-Mar-15	Addition of Subgroup Analysis - Including Gender and Race/Ethnicity
6-Oct-15	Minor formatting changes, added power for selected secondary analyses and subgroup analyses.
16-Dec-15	Section D. Subgroup Analysis - Including Gender and Race/Ethnicity. Clarified the will NOT have enough power to detect treatment effects among subgroups.
1-Dec-17	Per DSMB meeting 11OCT2017, the interim and futility analysis will not be performed. Clarified in the plan.
28-Dec-18	Clarification to the SAP - Combining sites with low enrollment and influence of symptomatic medication of the primary outcome, section 4C.