STATISTICAL ANALYSIS PLAN (SAP)

Protocol Title	**A Phase 3, Twelve-week, Multi-Center, Multinational, Randomized, Double-Blind, Double-Dummy, Parallel Group Study to Determine the Efficacy, Safety and Tolerability of P2B001 Once Daily Compared to its Individual Components in Subjects With Early Parkinson's Disease and to a Calibration Arm of Pramipexole ER**
Protocol Date:	**October 7, 2020, Version 3.0**
SAP Date:	**October 21, 2021, Version 2.0**
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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ADL	Activities of Daily Living
AR	Autoregressive
ARH	Heterogeneous Autoregressive
ATC	Anatomical Therapeutic Chemical Classification
ATC2	Therapeutic Subgroup (ATC2)
ATC4	Chemical Subgroup (ATC4)
BP	Blood Pressure
CDMS	Clinical Data Management System
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CGR	Country/Geographical Region
CGR1	Pooled Country Geographical Region
CHS	Heterogeneous Compound Symmetry
CO	Completers Analysis Set
CR	Controlled Release
CRO	Contract Research Organization
CS	Compound Symmetry
CSH	Heterogeneous Compound Symmetry
CSSRS-BL	Columbia Suicide Severity Rating Scale - baseline
CSSRS-SLV	Columbia Suicide Severity Rating Scale – since last visit
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EM	Expectation-Maximization
EMC	Eligibility Monitoring Committee
ER	Extended Release
ESS	Epworth Sleepiness Scale
EST	Early Study Termination
ETT	Early Treatment Termination
FCS	Fully conditional specification
H&Y	Hoehn and Yahr
HR	Heart Rate
HRQOL	Health-related quality of life
IP	Investigational Product
IMP	Investigational Medicinal Product
IR	Immediate Release

Abbreviation	Description
IRB	Institutional Review Board
ICD	Impulse control disorders
ITT	Intent to Treat
GI	Gastrointestinal
LDM	Lead Data Manger
LOV	Last Observed Value
LSM	Least Square Means
MAO	Mono Amine Oxidase
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MG	Milligram
mITT	Modified Intent to Treat
ML	Maximum-Likelihood
MMSE	Mini Mental State Exam
OH	Orthostatic Hypotension
PCS	Potentially Clinically Significant
PD	Parkinson’s Disease
PDQ39	Parkinson’s Disease Questionnaire 39
PI	Principal Investigator
PT	Preferred Term
QA	Quality Assurance
QUIP	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease
REML	Restricted Maximum-Likelihood
RR	Respiratory Rate
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SDV	Source Data Verification
SOC	System Organ Class
ST	Safety Analysis Set
TEAE	Treatment Emergent Adverse Event
TFL	Table Figure Listing
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Protocol P2B001/003, (A Phase 3, Twelve-week, Multi-Center, Multinational, Randomized, Double-Blind, Double-Dummy, Parallel Group Study to Determine the Efficacy, Safety and Tolerability of P2B001 Once Daily Compared to its Individual Components in Subjects With Early Parkinson's Disease and to a Calibration Arm of Pramipexole ER). When differences exist in descriptions or explanations provided in the Study Protocol and this SAP, the SAP prevails.

The purpose of this SAP is to outline the planned analyses to support the completion of the Clinical Study Report (CSR). The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support further clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP will be identified in the CSR.

This SAP was written and approved prior to study unblinding. Furthermore, the Author of this SAP as well as all personal approving this SAP are currently fully blinded to the randomization scheme.

Pharma Two Be would like to emphasize three topics of relevance to this study:

- Randomized Subjects Early Study Terminated During Screening/Baseline Visits: Due to a "just-in-time" shipping strategy, randomization was done at the end of screening period to allow shipping of the kit to the site. Study monitoring identified that approximately 4% to 5% of randomized subjects early terminated the study following randomization but prior to first dose which was planned to be consumed during the day after baseline visit. For more detailed please see Section 5.2.
- COVID-19 Pandemic: Due to COVID-19 pandemic, a total of approximately 8 subjects have had their study visits remotely and therefore Motor UPDRS evaluations could not be performed (See Section 5.3).
- Potential Unblinding Incident: An incident occurred during the conduct of this study wherein a total of 41 kits, from study medication kit Batches 353007 and 353007-3, were shipped to multiple clinical sites with potentially unblinding packing lists between March 2020 and December 2020.

  Following a full audit conducted by two expert auditing companies, ProPharma Group and Lachman Consultants, during the period of May 24, 2021, to June 30, 2021, Pharma Two B has concluded that the study blind remains intact, and that there were no compromises which would affect the integrity of the study data or bias interpretability of the study results and conclusions.

In the Type C response letter dated 29Sep2021, the Division requested that "*In addition to the planned analysis of the primary efficacy outcome, Pharma Two B provides a sensitivity analysis for the possible impact of the potentially unblinded clinical supplies*". Pharma Two B accepts the Division's request and provides this sensitivity analysis plan in Section 16.4.6.

2 STUDY OBJECTIVES

Pharma Two B intends to show that:

1. P2B001 has superior efficacy as compared to each of its components.
2. P2B001 is safe and tolerable.
3. P2B001 has descriptively comparable efficacy as well as safety benefits as compared to marketed pramipexole ER (here and after **pramipexole ER**, **PramiER**).

2.1 PER-PROTOCOL PRIMARY OBJECTIVE

To determine the superiority of P2B001 0.6/0.75 mg as compared to its individual components in the change of total UPDRS score (defined as sum of parts II and III, scores (0-160)).

2.2 PER-PROTOCOL SECONDARY OBJECTIVES

1. To determine the superiority of P2B001 0.6/0.75 mg as compared to pramipexole ER in the change of Epworth Sleepiness Scale (ESS) score.
2. To determine the efficacy of P2B001 0.6/0.75 mg as compared to its individual components in the change of Total PDQ39 score.
3. To determine the efficacy of P2B001 0.6/0.75 mg as compared to its individual components in the change of ADL UPDRS (part II) score.
4. To determine the efficacy of P2B001 0.6/0.75 mg as compared to its individual components in the change of motor UPDRS (part III) score.
5. To determine the efficacy of P2B001 0.6/0.75 mg as compared to its individual components in the CGI-S responder's analysis (change from baseline ≥1 CGI-S points).

2.3 PER-PROTOCOL EXPLORATORY OBJECTIVES

1. To evaluate the superiority of P2B001 0.6/0.75 mg compared to its individual components in the following endpoints:
   - ✓ Change in each of the 8 PDQ39 subscales scores.
   - ✓ Change in the score of Health-Related Quality of Life (HRQOL) SF-12v2 questionnaire.
   - ✓ Clinical Global Impression of Improvement (CGI-I).
2. To evaluate the superiority of P2B001 0.6/0.75 mg over pramipexole ER with respect to the following outcome measures:
   - ✓ Proportion (%) of patients with ESS score >10.
   - ✓ Proportion (%) of patients with ESS Score <10 at baseline and ESS score >10.
   - ✓ 3-Months rate of total number of adverse events.

- ✓ Change in the differences in systolic and diastolic blood pressure measured during supine and standing positions.
- ✓ Proportion (%) of patients with both symptomatic/non-symptomatic Orthostatic Hypotension.
- ✓ 3-Months rate of total number of both symptomatic/non-symptomatic Orthostatic Hypotension.
- ✓ Proportion (%) of patients with symptomatic Orthostatic Hypotension.
- ✓ 3-Months rate of total number of symptomatic Orthostatic Hypotension.
- ✓ Proportion (%) of patients with daytime sleepiness/drowsiness related AE's.
- ✓ Proportion (%) of patients with gastrointestinal (GI) adverse events
- ✓ Proportion (%) of patients presenting neurological adverse events
- ✓ Change in the score of Orthostatic Hypotension Symptoms Assessment (OHSA) question1.

3. To descriptively evaluate the comparability of P2B001 0.6/0.75 mg with reference to the calibration arm (pramipexole ER) in total UPDRS score (defined as sum of parts II and III, scores (0-160)).

   Note that no formal efficacy comparisons will be made between the calibration arm of pramipexole ER to the other three treatment arms.

2.4 PER-PROTOCOL SAFETY & TOLERABILITY OBJECTIVES

The safety profile of the test product and comparators will be evaluated by changes in the safety parameters, including adverse events, concomitant medications, vital signs, laboratory parameters, physical and neurological examinations, ECGs, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease- Rating Scale (QUIP-RS), Columbia Suicide Severity Rating Scale (CSSRS), Orthostatic Hypotension Symptoms Assessment (OHSA) question 1 and Epworth Sleepiness Scale (ESS).

Tolerability will be assessed by percentage of subjects that complete the trial on treatment assigned.

2.5 PER-PROTOCOL SAMPLE SIZE AND POWER CONSIDERATIONS

The study was powered to allow achieving two goals:

1. To demonstrate the superiority of P2B001 0.6/0.75mg compared to its individual components in the primary endpoint, the change from baseline to Week 12/Treatment Termination in total UPDRS score:

- ✓ The power to meet the primary endpoint was estimated based on simulation runs assuming equal arms size of P2B001 0.6/0.75mg and its individual components as well as repeated UPDRS measurements at baseline, week 4, week 8 and week 12.
- ✓ The expected STD of the change from baseline was assumed to be 6.0 UPDRS points.
- ✓ The expected treatment effect of P2B001 0.6/0.75mg is 3 UPDRS points over rasagiline 0.75mg and 2.25 UPDRS points over 0.6mg pramipexole.
- ✓ Sequential correlations between changes from baseline will be 0.7 and 0.49 between these obtained at week 4 and at week 12.
- ✓ Missing observations rate of 10% occurring at random.
- ✓ The statistical model used in the simulation study was the Mixed Model for Repeated Measures (MMRM) (SAS® MIXED procedure with REPEATED sub-command) testing two contrasts: P2B001 0.6/0.75mg vs. rasagiline 0.75mg and P2B001 0.6/0.75mg vs. pramipexole 0.6mg at Week 12/Treatment Termination.
- ✓ In order to consider the study as successful both tested contrasts have to be statistically significant at 5% two-tailed each.

The simulation indicates that a total of 150 subjects per group treated with P2B001 0.6/0.75mg, rasagiline 0.75mg or pramipexole 0.6mg will provide 87.6% power to detect a statistically significant effect size favoring P2B001 0.6/0.75mg by 3 UPDRS points over rasagiline 0.75mg and 2.25 UPDRS points over pramipexole 0.6mg.

2. To demonstrate the superiority of P2B001 0.6/0.75mg over pramipexole ER in the first secondary endpoint, namely, the change from baseline to Week 12/Treatment Termination in the ESS:
   - ✓ The power to meet this secondary endpoint was estimated using the two-sample t-test for mean difference at a two-sided alpha of 5% (SAS® POWER procedure).
   - ✓ The expected STD of the change from baseline was assumed to be 3.0 ESS points.
   - ✓ The expected treatment effect of P2B001 0.6/0.75mg over pramipexole ER is 1.5 ESS points.

- ✓ According to the gate keeping method for multiple endpoints while testing for the secondary endpoints, this secondary endpoint will be considered as met only in the case that both primary endpoint contrasts as well as the P2B001 0.6/0.75mg over Pramipexole ER comparison in the change from baseline to Week 12/Treatment Termination in the ESS will be met at two-tailed alpha level of 5% each.

This analysis indicates that a total of 150 subjects per group treated with P2B001 0.6/0.75mg and 75 subjects treated with pramipexole ER, considering the above assumptions, will provide a power of 94.1% to detect a statistically significant effect size at the magnitude of 1.5 ESS units or more at a two-sided alpha level of 5%.

2.6 BLINDED SAMPLE SIZE RE-ASSESSMENT

2.6.1 Protocol Pre-Defined Plan

To examine whether the variance estimate used in power calculations for the primary endpoint was adequate, an assessment of the variance magnitude will be performed after at least 1/3 of the subjects complete the study treatment period. The EM algorithm of Gould and Shih [*Communications in Statistics. A Theory and Methods, 21, 2833-2853, 1992*], will be applied to estimate the variance of the change from baseline to Week 12/Treatment Termination in total UPDRS score, without breaking the blind. In the case that the variance estimate will be found to be larger than the one projected, the sponsor reserves the right to up-size the study via a protocol amendment.

2.6.2 Notes on the Gould and Shih Algorithm

The blinded variance estimate was performed according to the Expectation-Maximization (EM) algorithm described in Gould (1992), to estimate the variance of the primary endpoint, without breaking the blind.

Posch et al [*Statistical Methods in Medical Research 2018, Vol. 27(6) 1830–1846)*] concluded that although this interim estimate is not consistent *[(Govindarajulu Z. Robustness of sample size re-estimation procedure in clinical trials (arbitrary populations). Stat Med 2003; 22: 1819–1828)*] and has a positive bias if the alternative hypothesis holds, the bias is negligible for effect sizes typically observed in clinical trials [Friede T and Kieser M. Blinded sample size re-estimation in superiority and noninferiority trials: bias versus variance in variance estimation. Pharmaceut Stat 2013; 12: 141–146]. Furthermore, sample size reassessment based on the total variance has no relevant impact on the type I error rate in parallel group superiority trials [Kieser M and Friede T. Simple procedures for blinded sample size adjustment that do not affect the type I error rate. Stat Med 2003; 22: 3571–3581] and achieves the target power well.

Pritchett et al [*Statistics in Biopharmaceutical Research: November 2015, Vol. 7, No. 4*] also concluded that data from a clinical trial with a sample size adaptation following a blinded sample size reassessment procedure can be used as whole without adjustment and the nominal level can be used as it is for final data analysis.

FDA's (2019) adaptive designs guidance encouraged the use of blinded sample size reassessment based on non-comparative data and concluded that "*In general, adequately prespecified adaptations based on non-comparative data have no effect or a limited effect on the Type I error probability. This makes them an attractive choice in many settings, particularly when uncertainty about event probabilities or endpoint variability is high.*"

2.6.3 Results and Conclusions

Sample size reassessment was performed at the time dictated by the protocol. The EM algorithms used in this analysis suggested an SD estimate of **5.354** as compared to **6.0** UPDRS units used in the protocol for study power assessment.

However, given the under-estimation factor of the algorithm, estimated under the expected study conditions -0.855, it is not unreasonable to assume the STD value of **6.209**, somewhat higher from that assumed in the protocol (6.0).

In conclusion, the analyses summarized in the report dated July 21, 2019, provided no clear evidence that advocated sample size modification for Study P2B001/003.

3 STUDY METHODS

3.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

This study is a phase 3, twelve-week, randomized, double-blind, double-dummy, 4-arm, parallel group, multi-center, multinational study to determine the efficacy, safety and tolerability of P2B001 in subjects with early Parkinson's disease as compared to its individual components and compared to a calibration arm of pramipexole ER.

A total of approximately 525 eligible subjects with early PD are randomized to treatment with P2B001 0.6/0.75 or pramipexole 0.6 mg once daily, or rasagiline 0.75 mg once daily, or pramipexole ER titrated to optimal dose (1.5, 3.0 or 4.5mg) using a randomization scheme of 2:2:2:1, respectively. Randomization will take place following the completion of all screening procedures including subject approval by both site principal investigator (PI) and the central Eligibility Monitoring Committee (EMC). Subjects will be recruited from approximately 70 sites in North America and Europe.

3.2 DOSING REGIMEN

Each subject will be asked to take one capsule and 1-3 tablets once daily. The capsules will contain either P2B001 0.6/0.75 mg or pramipexole 0.6 mg or rasagiline 0.75 mg or matching placebo. The tablets will contain either Pramipexole ER or matching placebo.

- P2B001 pramipexole dihydrochloride 0.6mg/Rasagiline 0.75 mg Once Daily + Placebo of Pramipexole ER.
- Pramipexole dihydrochloride 0.6 mg Once Daily (PPX 0.6) + Placebo of Pramipexole ER.
- Rasagiline 0.75 mg Once Daily (RAS 0.75) + Placebo of Pramipexole ER.
- Pramipexole ER individually titrated to optimal dose + Placebo of P2B001.

3.3 STUDY STRUCTURE

3.3.1 Up-Titration Phase

Up-Titration phase: A 3-6 week double blind, double dummy titration phase with pramipexole ER or matching placebo. During this phase subjects will also take 1 capsule of P2B001/RAS 0.75/PPX0.6/Placebo which does not need titration. For the first 3 weeks the titration of the pramipexole ER will be increased by weekly increments up to a daily dose of 1.5 mg as follows: 0.375, 0.75 and 1.5 mg. If needed, between weeks 3 and 6, the titration can continue to a daily dose of 3.0 mg or 4.5 mg of pramipexole ER or matching placebo or reduced to a minimum of 1.5mg with the final level determined based on achieving satisfactory efficacy and tolerability. On completion of the dose-titration phase (end of week 6), the minimum therapeutic dose of Pramipexole ER 1.5 mg per day (or placebo) must be achieved by all the patients. The treatment with study medications of patients who cannot achieve this dosage will be discontinued, but the subject will be requested to continue with all the study visits.

3.3.2 Maintenance Phase

Maintenance phase: Once the final dose level has been reached for the pramipexole ER, the subject will continue at that dose, together with the once daily P2B001/RAS 0.75/PPX0.6/Placebo capsule, until the end of Week 12.

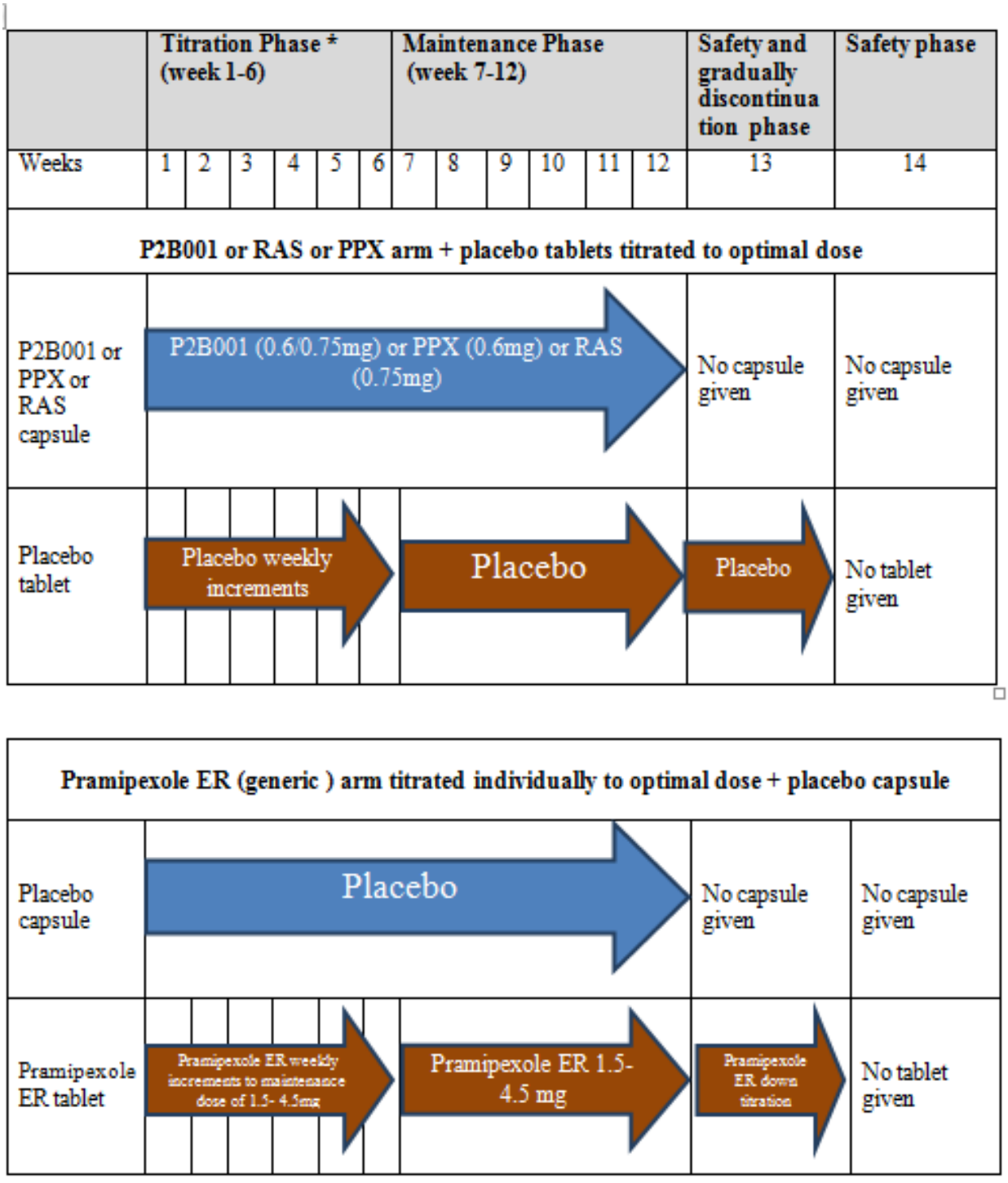
3.3.3 Down-Titration Phase

Down-titration phase (while blinding is maintained): a 7 day gradual down titration of pramipexole ER or matching placebo. The down titration should be done by reducing the dose every two days by half (except for subjects taking 4.5 mg, these should reduce the dose to 3.0 mg and then continue to reduce by half every two days). There is no treatment with once daily P2B001/RAS 0.75/PPX0.6/Placebo capsules during this period.

3.3.4 Safety Follow-Up Phase

Safety follow-up phase: a 7 days period of no treatment of pramipexole ER and 14 day period of no treatment for the P2B001/RAS 0.75/PPX0.6/Placebo capsule.

3.3.5 Study Design Scheme and Schedule of Activities



*Titration phase: Subjects can stop titration of pramipexole ER or placebo at 1.5 mg or can continue titration and increase the dose to 3.0 or 4.5 mg to optimal dose or decrease back to 3.0 or 1.5 mg. The dosage level achieved at the end of the titration phase (end of week 6) is then held constant during the maintenance phase ending at the end of week 12.

Visit Number	**1**	**2**	**3**	**3.5******	**4**	**5**	**6**	**7**
Visit Type	**Screening**	**Baseline**	**End of Week 3**	**End of Week 4**	**End of Week 5**	**End of Week 8**	**End of Week 12**	**End of Week 14**
Time	**-28 days to day 0****	**Day 1**	**21 ±2 days**	**28±2 days**	**35 ±2 days**	**56 ±2 days**	**84 ±2 days**	**98 ±2 days**
ACTIVITIES								
Written Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria	X							
Modified H&Y Stage	X							
Mini Mental State Exam (MMSE)	X							
Medical History & Demographics	X							
Complete Physical and Neurological Examination	X							
Symptom-directed physical and neurological Examination								X
Laboratory tests (serum biochemistry, hematology, urinalysis, serum pregnancy test)*	X***							X
Urine pregnancy test		X						
ECG	X	X						X
Randomization to Study Medication/Enrollment ID Assignment	X as soon as subject approved by PI and EMC							
Distribute Dosing Instruction Cards and emergency contact cards		X						
Dispense Study Drug		X						
Phone call for evaluation of Pramipexole ER (or placebo) dose				X****				
Vital Signs/Height/Weight*****	X	X			X	X	X	X
On-site evaluation of Pramipexole ER (or placebo) dose			X		X			
Concomitant Medication Review	X	X	X	X	X	X	X	X
Adverse Event Review	X	X	X	X	X	X	X	X
UPDRS Part III	X	X			X	X	X	
UPDRS Part II		X			X	X	X	
Columbia Suicide Severity Rating Scale (CSSRS)	X	X	X		X	X	X	X
QUIP-RS		X	X		X	X	X	X

Visit Number	1	2	3	3.5****	4	5	6	7
Visit Type	**Screening**	**Baseline**	**End of Week 3**	**End of Week 4**	**End of Week 5**	**End of Week 8**	**End of Week 12**	**End of Week 14**
Time	**-28 days to day 0****	**Day 1**	**21 ±2 days**	**28±2 days**	**35 ±2 days**	**56 ±2 days**	**84 ±2 days**	**98 ±2 days**
PDQ-39		X					X	
Epworth Sleepiness Scale (ESS)		X			X	X	X	
Clinical Global Impression-severity (CGI-S)		X					X	
Clinical Global Impression-improvement (CGI-I)					X	X	X	
HRQOL SF-12v2		X					X	
OHSA question 1 ******		X			X	X	X	
Drug Accountability/ Compliance					X	X	X	X
Collect study drug kit from previous month					X	X	X	X
Trial Completion								X

* Lab tests for renal/hepatic functions for subjects with mild renal and or mild hepatic impairment will be performed at visits 4 and 5.

** The maximal interval between the screening and baseline visits can be extended to 35 days, however, additional Sponsor approval will be required. 35 – 90 days may be approved but a new collection of screening laboratory samples will be required to verify eligibility prior to baseline.*** Coagulation will also be performed at screening to determine eligibility and at visits 4 and 5 for subjects with mild hepatic impairment.

**** An unscheduled on-site visit may be conducted per PI's or sub-Investigator's decision to evaluate the new dose and consider the need for further dose increase.

*****height will be measured only at screening

****** OHSA question 1 will be completed only by subjects experiencing orthostatic hypotension

4 STUDY CONDUCT AND PROCEDURES

4.1 STUDY PERIOD

The study duration per subject is 14 weeks in addition to up to 28 days for screening.

4.2 STUDY PROCEDURES

4.2.1 Detailed Study Plan

The study includes 7 visits. The first visit will allow screening of potential subjects that will participate in the study. This period of time between the screening visit and enrollment of a subject to the study is named the screening phase. The treatment phase is when subjects are receiving treatment with the study drugs. During the treatment phase, subjects' condition will be evaluated every 3-5 weeks (visits 2-6). The first 6 weeks of the treatment period will include a titration of the Pramipexole ER dose or its placebo to optimal dose (titration phase). One capsule a day of P2B001/PPX 0.6/RAS 0.75/Placebo will be taken at this time without any need for titration. This will be followed by a maintenance phase ending at the end of week 12. The safety follow up phase will start after week 12 which will include a week (week 13) of no treatment of the P2B001 or its components and a down-titration of pramipexole ER or its placebo. Week 14 will include no treatment at all. The end of the study drug treatment and a follow up safety visit will be performed at the end of week 14 (visit 7).

4.2.2 Visit 1 - Screening Visit

Prior to performing any study activity, the subject will be thoroughly informed on all aspects of the study. The subject will be requested to sign an Ethics Committee/investigational Review Board (EC/IRB) approved informed consent form, after which a unique subject number will be assigned to the subject.

Adverse events will be recorded after the signing of the informed consent of enrolled subjects. Subjects will be assessed for study eligibility by the Investigator at the screening visit. Subject eligibility will be assessed based on clinical procedures:

- Medical history – Complete medical history including PD history
- Complete physical and neurological examination
- Vital signs (HR, BP RR and temperature), height, weight, and ECG
- Previous and concomitant drug history (record of drugs used 3 months prior to study)
- Laboratory tests, including hematology, chemistry, urinalysis, coagulation and a serum pregnancy test for women of childbearing potential (see Appendix II)
- Mini Mental State Exam (MMSE)
- Modified H&Y staging

- UPDRS part III
- UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria
- CSSRS-BL

After completion of all the testing for the assessment of eligibility, it will be decided by the Investigator whether the subject is eligible for the study. For a subject to be eligible all the inclusion criteria must be met and none of the exclusion criteria must apply. Therefore, all the results from the screening procedures must be available before determining a subject's eligibility. Subjects found eligible will be further reviewed by a central eligibility monitoring committee. The maximal interval between the screening and baseline visits is 28 days that can be extended up to 35 days, however, additional Sponsor approval will be required. Extension beyond 35 days and up to 90 days may be approved but will require a new collection of screening laboratory samples at an unscheduled visit prior to baseline. Subjects that are screen failures may rescreen for the study. If the rescreening visit is within 28 days (or 35 days with sponsor approval) of the original blood testing, the screening number remains the same and the blood draw does not need to be repeated, unless it is the reason for the screening failure.

Subjects complying with inclusion/exclusion criteria will be randomly assigned to one of the four treatment groups by a central website-based computer program using Randomization Trial Supply Management (RTSM). A randomization form must be completed via the RTSM as soon as possible after subject eligibility was confirmed in order to trigger shipment of investigational product for this subject.

4.2.3 **Visit 2 - Baseline**

The time between visit 1 (screening), and visit 2 (baseline), will be no less than 24 hours and no more than 28 days (or up to 90 days with sponsor approval). In this visit a medication kit will be dispensed to him/her together with a leaflet of instructions for use. The subject will be given an emergency contact card with 24 hour contact numbers. The subject will be instructed to keep the contact card with him/her at all times. The following activities will be performed:

- Dispensation of study medication kit
- Vital signs (HR, BP RR and temperature), weight and ECG
- Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Adverse events review
- Inclusion/Exclusion criteria review
- Study drug dispensing and dosing instructions
- UPDRS II and III questionnaire
- CSSRS- SLV questionnaire
- CGI-S questionnaire

- PDQ39 questionnaire
- ESS questionnaire
- QUIP-RS questionnaire
- HRQOL SF-12v2
- Orthostatic hypotension scale question 1 for subjects with OH

The treatment should be started according to the dosing instructions the day after the baseline visit.

4.2.4 Visit 3 (Week 3)

At the end of week 3 ±2 days subjects will be required to visit the clinic for titration evaluation regarding their satisfaction and tolerability with the 1.5 mg dose of Pramipexole ER (or placebo). The dose may remain 1.5 mg or be increased to 3.0 mg. Additionally, the subject will continue to take 1 capsule a day of P2B001/PPX 0.6/RAS 0.75/placebo. The following activities will be performed:

- On-site evaluation of Pramipexole ER (or placebo) dose.
- Concomitant medications
- Adverse events review
- CSSRS-SLV questionnaire
- QUIP-RS questionnaire

4.2.5 Visit 3.5 (Week 4 Phone Call)

At the end of week 4 a phone call to the subject will be conducted by the PI or sub-Investigator regarding the subject's satisfaction and tolerability of the treatment and the possible need for increase of the dose. During this phone call a review of adverse events and concomitant medications will also be done. In addition, if the PI or sub-Investigator deem necessary, an unscheduled visit for a titration evaluation may be conducted at this time.

4.2.6 Visit 4 (Week 5)

Visit 4 will take place 5 weeks after the baseline visit ±2 days. The following activities will be performed:

- Evaluation of the pramipexole ER/placebo dose which may be changed if necessary, only until the end of the next week, week 6.
- Vital signs (HR, BP RR and temperature) and weight
- Concomitant medications
- Adverse events review
- Study drug accountability
- Collection of the titration kit, (Weeks 1-4)
- UPDRS II, III
- CSSRS-SLV questionnaire

- QUIP-RS questionnaire
- ESS questionnaire
- CGI-I questionnaire
- Orthostatic hypotension scale question 1 for subjects with OH
- Laboratory tests for hepatic or renal function for subjects with mild hepatic failure or mild kidney failure respectively.

4.2.7 Visit 5 (Week 8)

Visit 5 will take place 8 weeks after the baseline visit and start of medication treatment ±2 days. The following activities will be performed:

- Vital signs (HR, BP RR and temperature) and weight
- Concomitant medications
- Adverse events review
- Study drug accountability
- Collection of the maintenance kit (Box 1 of 2, weeks 5-8)
- UPDRS II, III
- CSSRS-SLV questionnaire
- QUIP-RS questionnaire
- ESS questionnaire
- CGI-I questionnaire
- Orthostatic hypotension scale question 1 for subjects with OH
- Laboratory tests for hepatic or renal function for subjects with mild hepatic failure or mild kidney failure respectively.

4.2.8 Visit 6 – Treatment Termination (Week 12)

Visit 6 will be performed at the end of the treatment phase, 12 weeks ±2 days after the baseline visit. The following activities will be performed:

- Vital signs (HR, BP RR and temperature), weight
- Concomitant medications
- Adverse events review
- Study drugs accountability
- Collection of maintenance kit (Box 2 of 2 Weeks 9-12)
- UPDRS II and III questionnaire
- CSSRS-SLV questionnaire
- CGI-S questionnaire
- CGI-I questionnaire
- PDQ39 questionnaire
- ESS questionnaire
- QUIP-RS questionnaire

- HRQOL SF-12v2
- Orthostatic hypotension scale question 1 for subjects with OH

4.2.9 Visit 7 – Safety Follow Up

A follow up safety visit will be performed 2 weeks ±2 days after the termination visit. Safety parameters will be evaluated, as follows:

- Symptom-directed physical and neurological examination
- Vital signs (HR, BP RR and temperature), weight and ECG
- Concomitant medications
- Adverse events review
- Study drugs accountability
- Collection of down titration kit (week 13)
- Laboratory tests, including hematology, chemistry, urinalysis and a serum pregnancy test for women of childbearing potential (see Appendix II)
- CSSRS-SLV questionnaire
- QUIP-RS questionnaire

4.2.10 Unscheduled Visits

If needed, an unscheduled visit may take place.

- Unscheduled visit for titration follow-up:
  During the titration phase an unscheduled visit may be conducted to assess the need to raise or lower the dose of pramipexole ER/or placebo. In addition to the dose evaluation, a review of adverse events and concomitant medications will be conducted. No other study activities will be performed at this visit unless safety considerations arise (see next section).
- Unscheduled visit for other reasons:
  An unscheduled visit may take place at any time during the study (e.g. PD symptoms or an AE that warrant personal evaluation). The following activities will be performed:
  - ✓ Vital signs (HR, BP RR and temperature) and weight
  - ✓ Concomitant medication
  - ✓ Adverse events review
  - ✓ Symptom-directed physical and neurological examination
  - ✓ Completion of any uncompleted efficacy or safety scales, as needed
  - ✓ The date and reason for the visit and any data generated will be documented in the eCRF.

4.2.11 Early Treatment/Study Termination Visit

There are two types of discontinuations in the study:

- ETT: Early Treatment Termination
- EST: Early Study Termination

Subjects who ETT/EST will be requested to undergo a treatment/study termination visit. The treatment termination visit can be conducted as part of the next scheduled study visit if it is within 5 days of treatment termination. If the next scheduled visit is more than 5 days away it is preferable, if possible, to schedule an "unscheduled" visit as soon as possible. All efforts should be made to schedule the early treatment/study termination visit as close to the treatment/study termination as possible. All activities listed in the treatment termination (visit 6) and safety visits (visit 7) will be performed at this visit. The entire study medication kit with all boxes and bottles left should be returned. The date and reason for the ETT and any data generated from the ETT visit will be documented in the eCRF.

Subject will be requested to continue all study scheduled activities as planned. If a subject refuse to take part in the scheduled study visits and activities, it will be documented as early study termination and the Investigator shall only follow up on any safety issues if needed.

4.2.12 Follow-up of Early Treatment Terminated (ETT) Subjects

Subjects ETT will be requested to continue with all study visits and activities as planned, for follow up, without taking any study medication. During these visits, all questionnaires and assessments will continue as planned for follow up. Accountability will be omitted since study drug was returned at the ETT visit.

Subjects may take rescue therapy during the follow-up visits; this will be documented in the concomitant medication list.

ETT subjects that decided later to stop their participation in the study will be requested to undergo a study termination visit. All activities listed in the treatment termination (visit 6) and safety visits (visit 7) will be performed at this visit.

4.3 STUDY POPULATION

4.3.1 Inclusion Criteria

Subjects must meet all the inclusion criteria to be eligible:

1. Subject is informed and given ample time and opportunity to think about his/her participation in this study and has given his/her written informed consent on an EC/IRB approved consent form.

2. Subject is willing and able to comply with all study requirements (protocol, clinic visits, procedures and medication administration).
3. Subject is male or female ≥35.0 years of age to ≤80.0 years of age at the time of enrollment
4. Subject has Parkinson's disease consistent with the UK Brain Bank Criteria and must have bradykinesia with sequence effect. If rest tremor does not exist must have prominent asymmetry of motor function.
5. Subject with disease duration less than 3 years since diagnosis.
6. Subject has a H&Y stage score of < 3.
7. Subject has a MMSE score ≥ 26.
8. Women of child-bearing potential (WOCBP)* must use a reliable method of contraception (e.g., oral contraceptive or long-term injectable or implantable hormonal contraceptive, double-barrier methods [such as condom plus diaphragm, condom plus spermicide foam, condom plus sponge], or intra-uterine devices) for the entire study duration, and must have a negative serum pregnancy test at Screening and negative urine pregnancy at baseline visit.
9. Subject was approved by a central Eligibility Monitoring Committee (EMC) based on suitability for the study, and his/her eligibility was confirmed by EMC signature on the Randomization Authorization Form (RAF).

*WOCBP are defined as any female who has experienced menarche and who is NOT permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

4.3.2 Exclusion Criteria

Subjects are not permitted to enroll in the study if any 1 of the following criteria is met.

1. Subject has previously participated in this study.
2. Subject has participated in another study of an investigational medicinal product (IMP) or a medical device within the last 30 days or is currently participating in another study of an IMP or medical device.
3. Subject has an atypical parkinsonian syndrome or secondary parkinsonism (e.g., due to drugs, toxins, metabolic disorders, encephalitis, cerebrovascular disease or degenerative disease).
4. Subject has a history of psychosis or hallucinations within the previous 12 months.
5. Subject has cognitive impairment in the judgment of the Investigator that excludes him/her from understanding consent or participating in the study.

6. Subject has previous exposure to levodopa or a dopamine agonist for longer than 4 weeks; if previous exposure was less than 4 weeks then it must not be within 2 months prior to the baseline visit.
7. Subject has previous exposure to a MAO-B inhibitor for longer than 4 weeks; if previous exposure was less than 4 weeks then it must not be within 3 months prior to the baseline visit.
8. Subject who has taken anticholinergic drugs for PD or amantadine for longer than 4 weeks; if previous exposure was less than 4 weeks then it must not be within 1 month prior to the baseline visit.
9. Subject who is taking non-selective MAO inhibitors.
10. Subject who is taking potent CYP1A2 inhibitors, e.g., Ciprofloxacin
11. Subject who is taking antitussive agent dextromethorphan.
12. Subject who is taking analgesic agents such as tramadol, meperidine, methadone and propoxyphene.
13. Subject who is taking strong 3A4 inducers, e.g., St. John's Wort or cyclobenzaprine (tricyclic muscle relaxant).
14. Subject who is taking dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide.
15. Marijuana or previous exposure to Marijuana during the last 30 days prior to the baseline visit or subject has a history of alcohol or drug abuse or dependence within the prior 12 months, according to Investigator judgment, (alcohol intake is limited to 1 glass or shot per day during the whole study taken not less than 3 hours before or after dosing.
16. Any relevant medical, surgical, or psychiatric condition, laboratory value, or concomitant medication which, in the opinion of the Investigator, makes the subject unsuitable for study entry or potentially unable to complete all aspects of the study.
17. Subject has severe or moderate renal impairment (creatinine clearance <50 mL/min) or on dialysis.
18. Subject has moderate (Child-Pugh categorization B, score 7-9) or severe (Child-Pugh categorization C, score 10-15) hepatic impairment (Lucey MR, 1997).
19. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ('Yes') to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (CSSRS) at Screening.
20. Subject has known hypersensitivity or intolerance to pramipexole or rasagiline or to any components or excipients of the test drug or placebo.
21. Subject who has a history of neuroleptic malignant syndrome.
22. Subject who is pregnant or breastfeeding.

23. Subject, who, for any reason, is judged by the Investigator or the EMC to be inappropriate for this study, including a subject who is unable to communicate or cooperate with the Investigator or who has/had a clinically significant illness or abnormal physical examination that may compromise safety of the subject during the trial or affect ability of the subject to adhere to study procedures.

A site will not be allowed to randomize subjects unless their diagnosis and suitability for the study has been confirmed and documented by both the Investigator and the EMC and they are deemed to be a satisfactory candidate by the EMC.

5 TREATMENT ASSIGNMENT, RANDOMIZATION AND BLINDING

5.1 RANDOMIZATION PROCEDURE

All subjects will be assigned a unique subject number at the screening visit (visit 1). The subjects found to be eligible for the study by both PI and the EMC will be randomized as soon as possible in order to trigger shipment of investigational medication to the site. At randomization, the subject will be given a unique randomization number which will be entered into the database but not used for subject follow-up. The same unique subject number allocated in the screening visit will continue to be the subject ID number for the rest of the study.

The randomization will be managed by a cloud-based Randomization and Trial Supply Management (RTSM) system of Medidata-Balance using a randomization list comprised of permuted blocks, with stratification by region. Allocation will be to the next available record in the randomization list which corresponds to the appropriate stratum. Medication will be assigned based on the treatment group allocated at randomization.

Study files will keep track of subject number and medication kit number. In case of medication kit loss or the patient ran out of drug for any reason the site can get a replacement medication kit by contacting the RTSM in order to get the appropriate medication kit number.

Randomization will take place following the completion of all screening procedures including subject approval by both site PI and the central EMC.

Subjects will be randomized to treatment with P2B001 0.6/0.75 (approximately 150 subjects), or pramipexole 0.6 mg once daily (approximately 150 subjects), or rasagiline 0.75 mg once daily (approximately 150 subjects), or pramipexole ER titrated to therapeutic optimal dose (approximately 75 subjects) using a randomization scheme of 2:2:2:1, respectively, stratified by region.

5.2 RANDOMIZED SUBJECTS EARLY STUDY TERMINATED DURING SCREENING/BASELINE VISITS

Due to a "just-in-time" shipping strategy, randomization was done at the end of screening period to allow shipping of the kit to the site. Study monitoring identified that approximately 4% to 5% of randomized subjects early terminated the study following randomization but prior to first dose which was planned to be consumed during the day after baseline visit. Reasons for early study termination included:

- Some subjects were randomized just prior to the COVID-19 pandemic during March 2020 and could not continue in the study due to restrictions that didn't allow patients to come to the hospitals during that time.
- Erroneous/premature randomization by PI due to mistaken use of RTSM system,
- Lack of EMC approval to randomize a subject
- Subject found ineligible during baseline visit.
- Withdrawal of consent / lost to follow-up between day of randomization (Visit 1, at end of screening procedures) and drug dispensation to be performed at study Day 1 (Baseline, Visit 2).

5.3 MISSING OBSERVATIONS DUE TO COVID-19

Due to COVID-19 pandemic a total of approximately 9 subjects have had their study visits remotely and therefore Motor UPDRS evaluations could not be performed.

5.4 BLINDING

Blinding will be maintained during the whole course of the study. The Investigators, study coordinators, and their staff at the study site, the sponsor's personnel and the personnel involved in subject assessment, monitoring, analysis and data management as well as the assigned Biostatistician (Shaul E. Kadosh, *StatExcellence* Ltd.) will all be blinded to the subject assignment. Specific, independent, unblinded study personnel from the CRO will be available to provide the DSMB with periodical safety reports and to release new IP supply in the RTSM system.

6 PROCEDURES PRIOR TO REVEALING OF THE BLIND

The Author of this SAP as well as all personnel approving this SAP are currently fully blinded to the randomization scheme.

Unblinding of the study database will be performed at end of study, when all subjects planned to be randomized into this study will undergo the Week 14 (Visit 7) Safety Follow-Up Visit and after all data base cleaning activities were completed.

Guidelines for procedures to be performed prior to revealing of the blind and immediately after revealing of the blind are provided in this section in **chronological order**:

6.1 "CLEAN" STUDY DATABASE

The study database will be considered to be "clean" when **all** of the below required tasks have been completed:

- Required data entered into eCRF
- Validations and manual review
- Queries were resolved
- SDV
- Medical review activities
- Data Management activities
- SAEs reconciliation
- Coding completed and approved by Sponsor
- External central laboratory data reconciliation
- External ECG data reconciliation
- List of ETTs that were classified by Sponsor as treatment related or non-treatment.
- List of disallowed medications use according to Determination of Disallowed Medications.
- List of subjects consuming rescue therapy (ATC code: N04, ANTI-PARKINSON DRUGS) post first study drug dose (see Definition of Date of First Study Drug Treatment and Rescue Therapy Post 1st Study Drug Dose).
- List of TEAEs of Special Interest will fully be identified prior to revealing of the blind.

- List of subjects flagged as with potential unblinding according to the potential unblinding incident described in Section 1 of this SAP. Note that this list will be provided to the assigned statistician after the receipt of the locked unblinded database. Since the entire kit of investigation product is dispensed to the subject prior to dosing, at the baseline visit, all study procedures were conducted after the potential unblinding document was sent to the site. Please note that since drug was dispensed at baseline visit, it implies that all post first dose assessments are subjected to the apparent potential unblinding and therefore exclusion of subjects will be performed on a by subject basis.

6.2 DETERMINATION OF DISALLOWED MEDICATIONS

The following medications are disallowed:

- Other investigational therapy (washout period 30 days prior to study entry, baseline visit)
- Previous MAO-B inhibitors, selegiline or rasagiline, for longer than 4 weeks or within the previous 3 months prior to baseline visit.
- Previous levodopa or dopamine agonists, for longer than 4 weeks or within the previous 2 months prior to baseline visit.
- Previous anticholinergic drugs for PD (such as benztropine, orphenadrine hydrochloride, biperiden, ethopropazine, procyclidine, trihexyphenidyl) or amantadine for longer than 4 weeks; if previous exposure was less than 4 weeks then it must not be within 1 month prior to the baseline visit.
- Subjects can take peripheral anticholinergic drugs (such as oxybutynin, orphenadrine citrate, tiotropium bromide etc..) if they are stable on low dose for at least 4 weeks prior to study entry, and without (or with minor) cognitive effects; however, once enrolled into the study use of new peripheral anticholinergic drugs is prohibited. Patients should be followed very closely for possible cognitive side effects.
- MAO inhibitors, such as phenelzine or tranylcypromine
- Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide.
- Ciprofloxacin or other CYP1A2 inhibitors: may affect rasagiline plasma concentrations.
- Antitussive agent Dextromethorphan.: co-administration with rasagiline may lead to psychosis.
- Analgesic agents such as tramadol, methadone, meperidine and propoxyphene due to risk of serotonin syndrome.
- St. John's Wort or cyclobenzaprine (tricyclic muscle relaxant).
- Marijuana or previous exposure to Marijuana during the last 30 days prior to the baseline visit.

A list with all concomitant medications, those initiated before or after study IP administration will be provided by the Sponsor to *StatExcellence* following the receipt of the blinded frozen database and prior to the receipt of the locked unblinded database.

6.3 RESCUE THERAPY POST 1ST STUDY DRUG DOSE

Rescue therapies taken post 1st study drug will be identified by ATC code: N04, ANTI-PARKINSON DRUGS.

6.4 DATABASE LOCKING PROCEDURES

6.4.1 Freezing Activities to be performed by PRA

1. All checks are performed as agreed in the DMP and confirmed via the data delivery checklist (pre delivery) – Freezing of subjects, No new SAE's etc.
2. Data Delivery Approval Form signed
3. LDM notifies Primary Programmer that checklist steps are completed and to proceed with extract
4. QC checks completed on extracted data
5. Primary programmer post extract
6. LDM confirms to Sponsor of successful extract
7. Sponsor to review data
8. Any updates/ queries required are reviewed by the LDM and applicable team members
9. Once all updates are made repeat steps 1-6.

6.4.2 Locking Activities to be Performed by PRA

1. Confirm all the activities have been completed for lock per the DMP and Pre Delivery checklist.
2. Data Delivery Approval Form signed by Sponsor (for Lock)
3. LDM notifies Primary Programmer that checklist steps are completed and to proceed with extract
4. QC checks completed on extracted data
5. LDM or LCDC requests Customer Support to Lock the CDMS, including removal of update and delete permissions from all Oracle tables housing external data
6. Systems Administrator will confirm that all System Users' access is removed, the CDMS is locked, and permissions removed from Oracle tables.
7. Sponsor and PRA team notified of successful lock.
8. In the event where an unlock is absolutely necessary, an unlocking and relocking Checklist will be created along with a data delivery approval form to be signed by Sponsor, Project Manager, Director of Data Management and Biostatistician.

6.5 DATABASE UNBLINDING ACTIVITIES BY PRA

Upon all subject data records are hard-locked and upon a specific signed request from Sponsor, the following will be performed:

1. The sponsor sends approval to UNBLIND the database.
2. Notification is sent to the Sponsor of the UNBLINDED data transfer.
3. PRA will incorporate the randomization information into the relevant SDTM domains.
4. PRA will transfer the hard-locked UNBLINDED database to Sponsor.

6.6 SPONSOR QA REVIEW OF RANDOMIZATION SCHEME

Following the receipt of the UNBLINDED SDTM but prior to initiation of any of the statistical analyses as per this SAP, Sponsor will verify the appropriateness of treatment assignment in the delivered SDTM database according to Sponsor's guideline named **"THE APPROPRIATENESS OF TREATMENT CODE ASSIGNMENT TO THE DATABASE OF P2B001/003 STUDY"**.

7 COMPARATIVE INTERIM ANALYSES

No comparative interim analysis was planned nor conducted for this clinical study.

8 DATA ANALYSES SETS

The following data analysis sets are defined for this study:

8.1 INTENTION-TO-TREAT ANALYSIS SET (ITT)

The ITT Analysis Set will include all randomized subjects, according to the treatment group to which they were originally randomized to.

8.2 MODIFIED INTENTION-TO-TREAT ANALYSIS SET (MITT)

The mITT Analysis Set is a subset of the ITT Analysis Set and includes subjects who were randomized, have taken at least one dose of study drug, and have at least one post-Baseline UPDRS (UPDRS II+III) measurement score at the planned scheduled visits. The mITT Analysis Set will use treatment according to the group to which subjects were originally randomized to. The mITT Analysis Set will serve as the principal analysis set for efficacy assessments.

8.3 COMPLETERS ANALYSIS SET (CO)

The Completers Analysis Set (CO) is a subset of the mITT Analysis Set excluding those subjects that failed to complete the 12 weeks of treatment according to the treatment group to which they were originally randomized.

8.4 PER PROTOCOL ANALYSIS SET (PP)

The Per Protocol Analysis Set (PP) is a subset of the CO Analysis Set excluding those subjects with important protocol violations according to the treatment group to which they were originally randomized. Note that important violations will be determined prior to unblinding.

8.5 SAFETY ANALYSIS SET (ST)

The Safety Analysis Set will include all randomized participants who took at least one dose of the study drug according to the treatment actually received. The ST analysis set will serve as the principal analysis set for safety assessments.

9 GENERAL ISSUES AND DEFINITIONS

9.1 DEFINITION OF POOLED COUNTRY/GEOGRAPHICAL REGION (CGR1)

For the purpose of statistical modelling, Canadian subjects (due to very low number) will be included in the US_NE stratum.

9.2 DEFINITION OF STUDY DRUG START/END DATES

9.2.1 Definition of Date of First Study Drug Treatment

Baseline visit (Visit 2) will be conducted no less than 24 hours and no more than 28 days (or up to 90 days with sponsor approval) following the completion of the screening period which is ended by the randomization procedure (for eligible subjects).

At Baseline visit (Visit 2), the study medication kit will be dispensed to the subject which will be instructed to initiate study medication consumption the day after the baseline visit.

DM domain of SDTM database includes two first study date variables: RFXSTDTC and RFSTDTC which should make a reference to a sole date to be considered in all related analyses of this study as date of first study treatment.

9.2.2 Definition of Date of Last Treatment Day in Study

Date of last treatment in study is defined as the latest treatment day among:

- P2B001/Placebo, or,
- Pramipexole ER/Placebo.

DM domain of SDTM database includes two last study date variables: RFXENDTC and RFENDTC which should make a reference to a sole date to be considered in all related analyses of this study as date of last study treatment.

9.2.3 Definition of Date of Last Dose of P2B001/Placebo

Once the final dose level has been reached for the pramipexole ER, the subject will continue at that dose, together with the once daily P2B001/RAS 0.75/PPX0.6/Placebo capsule, until the end of Week 12 (Visit 6).

The Date of Last Dose of P2B001/Placebo will be taken from SuppDS using QNAM='DSLDP2B' and QLABEL='Date of Last Dose of P2B001/Placebo'.

9.2.4 Definition of Date of Last Dose of Pramipexole ER/Placebo

Following the cessation of treatment with Pramipexole ER/Placebo, a 7-day gradual down titration of pramipexole ER or matching placebo will be initiated. The down titration should be done by reducing the dose every two days by half (except for subjects taking 4.5 mg, these should reduce the dose to 3.0 mg and then continue to reduce by half every two days).

The 'Date Last Dose of Pramipexole ER/Placebo' will be taken from SuppDS using QNAM=' DSLDPPX' and QLABEL='Date Last Dose of Pramipexole ER/Placebo'.

9.3 CALCULATION OF STUDY PERIODS

9.3.1 Calculation of Study Duration

Study duration calculated for each subject, given in days, will be calculated as the number of days elapsed from study consent to the date of study termination + 1 day.

9.3.2 Calculation of Treatment Duration

Treatment duration calculated for each subject, given in days, will be calculated as the number of days elapsed from first study drug treatment (See Definition of Date of First Study Drug Treatment) to the date of the latest study treatment date (See Definition of Date of Last Treatment Day in Study) + 1 day.

9.3.3 Calculation of P2B001/Placebo Treatment Duration

P2B001/Placebo treatment duration calculated for each subject, given in days, will be calculated as the number of days elapsed from first study drug treatment (See Definition of Date of First Study Drug Treatment) to the cessation date of treatment with P2B001/Placebo (See Definition of Date of Last Dose of P2B001/Placebo) + 1 day.

9.3.4 Calculation of Pramipexole ER/Placebo Treatment Duration

Pramipexole ER/Placebo treatment duration calculated for each subject, given in days, will be calculated as the number of days elapsed from first study drug treatment (See Definition of Date of First Study Drug Treatment) to the cessation date of treatment with Pramipexole ER/Placebo (See Definition of Date of Last Dose of Pramipexole ER/Placebo) + 1 day.

9.4 DEFINITION OF BASELINE (DERIVED) VALUES

At the end of the screening period, once a subject was found to be eligible for the study, he/she was randomized to receive one of the four study treatments. Later on, at baseline visit the study drug was dispensed and subject was instructed to start consuming the study medication on the next day.

The programming rule to identify baseline (derived) measurements is the latest assessment reported in the database for measurements taken up to first study drug uptake, including the day of the first study drug uptake. For subjects randomized but not treated, the date of randomization will be used.

Note that in TFLs reporting, "Baseline (Derived)" terminology will be used also for assessments planned to be taken only at screening (e.g. MMSE).

9.5 DEFINITION OF CHANGE FROM BASELINE (DERIVED)

The change from the baseline (derived) value is calculated for an individual subject in a specific parameter as the difference between the post-baseline value and the baseline (derived) value. Negative changes are indicative of decreases over time while positive changes reflect increases in the measured parameter.

9.6 DERIVATION OF PERCENT STUDY DRUG COMPLIANCE

- Study drug accountability (DA Domain) was based on the following:
  - ✓ No. Kits Dispensed each including:
    - 99 P2B/Placebo Capsules Dispensed (Blue)
    - 60 PPX ER 0.375/Placebo Tablets Dispensed (Yellow)
    - 240 PPX ER 1.5/Placebo Tablets Dispensed (Pink)
  - ✓ Returned PP2B/Placebo Capsules (Blue)
  - ✓ Returned PPX ER 0.375/Placebo Tablets (Yellow)
  - ✓ Returned PPX ER 1.5/Placebo Tablets Dispensed (Pink)
  - ✓ Lost PP2B/Placebo Capsules (Blue)
  - ✓ Lost PPX ER 0.375/Placebo Tablets (Yellow)
  - ✓ Lost PPX ER 1.5/Placebo Tablets Dispensed (Pink)
  - ✓ For each capsule/tablet (Blue, Yellow or Pink), the amount consumed was calculated as the amount dispensed minus the amount returned / lost.
- The amount of PPX ER tablets (Yellow and Pink) that a subject should have taken during the study was retrieved from PPX ER dose adjustment follow-up (Exposure as Collected - EC Domain) as follows:
  - ✓ For daily dose of 0.375: No. of days X 1 Yellow tablets.
  - ✓ For daily dose of 0.75 : No. of days X 2 Yellow tablets.
  - ✓ For daily dose of 1.5 : No. of days X 1 Pink tablets.

- ✓ For daily dose of 3 : No. of days X 2 Pink tablets.
- ✓ For daily dose of 4.5 : No. of days X 3 Pink tablets.

- The number of P2B/Placebo capsules (Blue) that a subject should have taken during the study (exposure as collected) was calculated as the number of days elapsed from first study dose date to the last one + 1 day.
- Accordingly, for each individual subject, the % compliance for each Blue, Yellow or Pink were calculated as the % of capsules/tables consumed divided by the number of capsules/tables that were expected to be consumed (exposure as collected) by a subject.

9.7 INCOMPLETE DATE IMPUTATION

In some cases, the database reported dates might be partial; the day of the month or the month might be missing. In such a case, full dates will be imputed; if the day will be missing it will be imputed as the 15 day of the month and if month was missing it was imputed as July of that year.

This rule will be implemented with the following exceptions:

- Full dates of randomization, date of first study dose and death dates, if occurred, are mandatory.
- Partial dates imputation of end date: In some cases, an imputation, as above described may lead to a situation in which end date will be before start date. In these cases, end dates will be imputed as start date + 1 day.

9.8 BY SUBJECT DATA LISTINGS

All data collected and accumulated in SDTM database of this study that are subjected to analyses according to this SAP will be displayed in by subject data listings.

9.9 CONVERGENCE ISSUES AND PRE-PLANNED STRATEGY

The Mixed Model for Repeated Measures (MMRM) (SAS® MIXED procedure with REPEATED sub-command) will be used for the analysis of several efficacy and safety endpoints. Data analysis will use as a default the unstructured covariance structure and the REML estimation method and degrees of freedom will be adjusted using the Kenward-Roger method.

In case that the model will not converge, the Maximum-Likelihood (ML) estimation method will be used instead of the default Restricted ML (REML). If the model still does not converge, then a simpler covariance structure with less parameters will be used, according to the following order: Heterogeneous Toeplitz, Heterogeneous Autoregressive(1) [ARH(1)], Heterogeneous Compound Symmetry (CSH), Autoregressive(1) [AR(1)], and Compound Symmetry (CS).

10 STUDY POPULATION SUMMARY

The ITT and the mITT analysis sets will be used to describe the study population. Descriptive statistics of these data will be provided by treatment group and overall.

10.1 SUBJECT DISPOSITION

Data from subjects who are screened/randomized, subjects who are screened/randomized and dosed, subjects in the pre-defined analysis sets, subjects who complete the study, subjects ETT, EST and subjects included in the ITT, mITT, CO and ST analysis sets will be summarized using descriptive statistics. Termination reasons will also be summarized by reason using descriptive statistics. The denominator for calculating the percentages will be the set of ITT.

10.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline characteristics including demography, general medical history, baseline physical examination, underlying PD disease characteristics, prior medications and baseline efficacy endpoints will be provided in summary tables broken down by treatment groups and overall.

For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median, minimum, and maximum) will be provided. For categorical variables, subject counts and percentages will be provided. Categories for missing data will be presented, if necessary.

10.3 MEDICAL HISTORY

The incidence (no. of patients) will be provided when broken down by primary system organ class (SOC) and by SOC and dictionary derived preferred term (PT) according to MedDRA dictionary. Subjects with at least 1 abnormal finding for each category will be summarized using descriptive statistics. Subjects will be counted only once in each category.

10.4 PRIOR, CONCOMITANT AND DISALLOWED MEDICATIONS

Prior, concomitant and disallowed medications use will be analyzed according to the ITT Analysis Set.

All prior and concomitant medications will be coded using the WHODRUG dictionary. Coded medications that ATC coding does not have all 4 levels will be assigned "**VARIOUS**" for the missing value levels.

The incidence of prior medications and separately those consumed concomitantly to study drug will be summarized using descriptive statistics by Therapeutic Subgroup (ATC2) and by ATC2 and Chemical Subgroup (ATC4).

Subjects will only be counted once in each Therapeutic Subgroup, and only once in each Chemical Subgroup.

- **Pre-Study Medications**: Analyses will include all coded medications that were initiated prior to first study IP administration regardless if continued during dosing period. Coded medications with missing start date will be included in this category.
- **Concomitant Medications**: Analyses will include coded medications that were consumed post start of study IP Administration regardless if drug initiation date was before or after first study dose. Uncertainty as to whether drug was consumed concomitantly due to missing medication start/end date will lead to consider medication as consumed concomitantly.
- **Disallowed Medications**: Disallowed medications use will be identified according to the procedure outlined in Determination of Disallowed Medications. A summary table displaying the number and percent of subjects, by treatment group, with concomitant medications use prior to study or during it will be provided accompanied by a reference data listing.
- **Rescue Therapy**: Rescue therapy consumption will be identified according to the procedure outlined in Rescue Therapy Post 1st Study Drug Dose. A summary table displaying the number and percent of subjects, by treatment group consuming rescue therapy post 1st study dose will be provided accompanied by a reference data listing.

10.5 PROTOCOL DEVIATIONS/CLARIFICATIONS

Protocol deviations and violations will be recorded on an ongoing basis and will be included in a DV domain in the SDTM database. Each captured term will be classified according to the below:

- EPOCH: Screening, Baseline, Blinded Treatment and follow-up.
- Category: Clarification or Deviation.
- Subcategory: Important (or not).
- Coded Terms: 01-Inclusion Criteria, 02-Exclusion Criteria, 03-Study Drug, 04-Assessment Safety, 05-Endpoint Data, 06-Visit Window, 07-Informed Consent, 08-Prohibited Medication, 09-Other or 10-Compliance.

An incidence table displaying the number and proportion (%) of subjects with at least one protocol deviation in each category and overall will be summarized using descriptive statistics. Individual subjects' listings will also be provided.

11 STUDY QUESTIONNAIRES AND SCORES DERIVATION

Listings provided to Sponsor in Excel and Word files were thoroughly reviewed by the Sponsor for derivation of scores used in the analysis prior to revealing of the study blind and all listed in this section were found to be accurately in line with the plan detailed in this section.

11.1 UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA (UPDSBB)

Parkinson's disease diagnosis will be confirmed for the purpose of the study as consistent with UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria. Expected answer to be obtained in database is "Yes". Response provided will be collected from SDTM FA dataset.

11.2 UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

The Unified Parkinson's Disease Rating Scale (UPDRS) questionnaire is composed of several parts. In this study, only parts II and III will be performed.

- **UPDRS Part II: Activities of Daily Living**

  Part II of the UPDRS disease rating scale is composed of **13** items as provided below. The total score (UPD901Derived) of this subscale can range from **0** to **52** as each item can get the value of 0, 1, 2, 3 or 4.

  If there are missing items in this subscale, the subscale total score (UPD901Derived) will be adjusted by dividing the obtained value by the total number of items that had responses and then multiplying by **13**. If more than 3 items are missing, the Part-II score will be considered invalid and will be set to missing value.

  The below identify the UPDRS Part II metrics (ADQS for QSCAT="UPDRS"):

Subcategory for Question	Question Short Name	Question Name
II.ACTIVITIES OF DAILY LIVING	UPD105	UPDRS II ADL: Speech
II.ACTIVITIES OF DAILY LIVING	UPD106	UPDRS II ADL: Salivation
II.ACTIVITIES OF DAILY LIVING	UPD107	UPDRS II ADL: Swallowing
II.ACTIVITIES OF DAILY LIVING	UPD108	UPDRS II ADL: Handwriting
II.ACTIVITIES OF DAILY LIVING	UPD109	UPDRS II ADL: Cut Food/Handle Utensil
II.ACTIVITIES OF DAILY LIVING	UPD110	UPDRS II ADL: Dressing
II.ACTIVITIES OF DAILY LIVING	UPD111	UPDRS II ADL: Hygiene
II.ACTIVITIES OF DAILY LIVING	UPD112	UPDRS II ADL: Turn Bed/Adj Clothes
II.ACTIVITIES OF DAILY LIVING	UPD113	UPDRS II ADL: Falling
II.ACTIVITIES OF DAILY LIVING	UPD114	UPDRS II ADL: Freezing When Walking
II.ACTIVITIES OF DAILY LIVING	UPD115	UPDRS II ADL: Walking
II.ACTIVITIES OF DAILY LIVING	UPD116	UPDRS II ADL: Tremor
II.ACTIVITIES OF DAILY LIVING	UPD117	UPDRS II ADL: Sensory Complaints
II.ACTIVITIES OF DAILY LIVING	UPD901Derived	Total UPDRS II ADL

- **UPDRS PART III: Motor Examination**

  Part III of the UPDRS disease rating scale is composed of **27** items as provided below. The total score (UPD902Derived) of this subscale can range from **0** to **108** as each item can get the value of 0, 1, 2, 3 or 4.

  If there are missing items in this subscale, the subscale total score (UPD902Derived) will be adjusted by dividing the obtained value by the total number of items that had responses and then multiplying by **27**. If more than **5** items are missing, the Part-III score will be considered invalid and will be set to missing value.

  The below identify the UPDRS Part III metrics (ADQS for QSCAT="UPDRS"):

Subcategory for Question	Question Short Name	Question Name
III.MOTOR EXAMINATION	UPD118	UPDRS III Motor: Speech
III.MOTOR EXAMINATION	UPD119	UPDRS III Motor: Facial Expression
III.MOTOR EXAMINATION	UPD120A	UPDRS III Motor: Tremor at Rest:Face Lips Chin
III.MOTOR EXAMINATION	UPD120B	UPDRS III Motor: Tremor at Rest:Hands: Right
III.MOTOR EXAMINATION	UPD120C	UPDRS III Motor: Tremor at Rest:Hands: Left
III.MOTOR EXAMINATION	UPD120D	UPDRS III Motor: Tremor at Rest:Feet: Right
III.MOTOR EXAMINATION	UPD120E	UPDRS III Motor: Tremor at Rest:Feet: Left
III.MOTOR EXAMINATION	UPD121A	UPDRS III Motor: Action Tremor:Hand: Right
III.MOTOR EXAMINATION	UPD121B	UPDRS III Motor: Action Tremor:Hand: Left
III.MOTOR EXAMINATION	UPD122A	UPDRS III Motor: Rigidity Neck
III.MOTOR EXAMINATION	UPD122B	UPDRS III Motor: Rigidity Upper Extrem: Right
III.MOTOR EXAMINATION	UPD122C	UPDRS III Motor: Rigidity Upper Extrem: Left
III.MOTOR EXAMINATION	UPD122D	UPDRS III Motor: Rigidity Lower Extrem: Right
III.MOTOR EXAMINATION	UPD122E	UPDRS III Motor: Rigidity Lower Extrem: Left
III.MOTOR EXAMINATION	UPD123A	UPDRS III Motor: Finger Taps: Right
III.MOTOR EXAMINATION	UPD123B	UPDRS III Motor: Finger Taps: Left
III.MOTOR EXAMINATION	UPD124A	UPDRS III Motor: Hand Grips: Right
III.MOTOR EXAMINATION	UPD124B	UPDRS III Motor: Hand Grips: Left
III.MOTOR EXAMINATION	UPD125A	UPDRS III Motor: Hand Pronate/Supinate: Right
III.MOTOR EXAMINATION	UPD125B	UPDRS III Motor: Hand Pronate/Supinate: Left
III.MOTOR EXAMINATION	UPD126A	UPDRS III Motor: Leg Agility: Right
III.MOTOR EXAMINATION	UPD126B	UPDRS III Motor: Leg Agility: Left
III.MOTOR EXAMINATION	UPD127	UPDRS III Motor: Arising from Chair
III.MOTOR EXAMINATION	UPD128	UPDRS III Motor: Posture
III.MOTOR EXAMINATION	UPD129	UPDRS III Motor: Gait
III.MOTOR EXAMINATION	UPD130	UPDRS III Motor: Postural Stability
III.MOTOR EXAMINATION	UPD131	UPDRS III Motor: Bradykinesia and Hypokinesia
III.MOTOR EXAMINATION	UPD902Derived	Total UPDRS III Motor

- **Total UPDRS score (Sum of Part II and Part III)**

  The **Total UPDRS Score** (ADQS for UPD903Derived) for this study is defined as the sum of scores of UPDRS Parts II (UPD901Derived) and III (UPD902Derived) as above defined. This score which ranges from **0** to **160** will be calculated only if both subscales scores are non-missing namely, Total UPDRS Score will be set to missing value if one or more of the below conditions is met:

  - ✓ For Part-II: If more than **3** items are missing.
  - ✓ For Part III: If more than **5** items are missing.

  The below identifies the Total UPDRS (ADQS for QSCAT="UPDRS"):

Subcategory for Question	Parameter Code	Parameter
II ADL AND III MOTOR	UPD903Derived	Total UPDRS

- **Total UPDRS (Sum of Part II and Part III) End of Week 12 Responder**

  A subject will be defined as a "Responder" in the case that the End of Week 12 improvement from baseline will be of 4 Total UPDRS points or more. Otherwise (precluding missing values) the subject will be defined as a "Non-Responder".

11.3 MODIFIED HOEHN & YAHR STAGING

The H&Y scale is a commonly used system for describing how the symptoms of Parkinson's disease progress. The original scale included stages 1 through 5. Since then, stage 0 has been added, and stages 1.5 and 2.5 have been proposed. This modified scale allocates stages from 0 to 5 to indicative of relative level of disability as described below:

- ✓ Stage 0: No signs of disease.
- ✓ Stage 1: Unilateral symptoms only.
- ✓ Stage 1.5: Unilateral and axial involvement.
- ✓ Stage 2: Bilateral symptoms. No impairment of balance.
- ✓ Stage 2.5: Mild bilateral disease with recovery on pull test.
- ✓ Stage 3: Balance impairment. Mild to moderate disease. Physically independent.
- ✓ Stage 4: Severe disability, but still able to walk or stand unassisted.
- ✓ Stage 5: Needing a wheelchair or bedridden unless assisted.

The below identifies the H&Y metric (ADQS for QSCAT="UPDRS"):

Subcategory for Question	Parameter Code	Parameter
V.MODIFIED HOEHN AND YAHR STAGING	UPD143	Modified Hoehn and Yahr Staging

11.4 CLINICAL GLOBAL IMPRESSION – SEVERITY SCALE (CGI-S)

This scale will be completed by the Investigator at baseline and at end of week 12/Treatment termination (Visit 6). The scale rates the subject's overall well-being, including the Parkinson's disease symptoms over the week before the visit. The CGI scale refers to the global impression of the subject and requires clinical experience with the syndrome under assessment.

The CGI-S scale is a 7-point scale that requires the clinician to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Efforts must be made to ensure that the same neurologist performs the CGI-S at all visits. Considering total clinical experience, a subject is assessed on severity of illness at the time of rating using a nominal scoring system with:

- ✓ 1=Normal, not at all ill
- ✓ 2=Borderline ill
- ✓ 3=Mildly ill
- ✓ 4=Moderately ill
- ✓ 5=Markedly ill
- ✓ 6=Severely ill
- ✓ 7=Extremely ill

The below identifies the CGI-S metric (ADQS for QSCAT="CGI"):

Subcategory for Question	Parameter Code	Parameter
PD	CGI0201	CGI-Severity

- **Definition of End of Week 12 CGI-S Responder**

  A subject experiencing an improvement of 1 point or more in change from Baseline (Derived) to End of Week 12 visit of the CGI-S will be classified as a "Responder" and a subject failing to meet this criterion will be classified as a "Non-Responder".

11.5 CLINICAL GLOBAL IMPRESSION – IMPROVEMENT SCALE (CGI-I)

This scale will be completed by the Investigator at end of weeks 5, 8 and 12/Treatment Termination (visits 4, 5 and 6). The scale rates the subject's overall well-being, including the Parkinson's disease symptoms over the week before the visit. Efforts must be made to ensure that the same neurologist performs the CGI-I at all visits

The CGI-I scale is a 7-point scale that requires the clinician to rate the improvement of the subject's illness relative to the baseline visit using a nominal scoring system with:

- ✓ 1=Very much improved
- ✓ 2=Much improved
- ✓ 3=Minimally improved
- ✓ 4=No change

- ✓ 5=Minimally worse
- ✓ 6=Much worse
- ✓ 7=Very much worse

The below identifies the CGI-S metric (ADQS for QSCAT="CGI"):

Subcategory for Question	Parameter Code	Parameter
PD	CGI0203	CGI-Improvement

- **Definition of End of Week 12 CGI-I Responder**

  A subject classified at the End of Week 12 visit with an improved scores of 1 or 2 will be classified as a "Responder" and a subject failing to meet this criterion will be classified as a "Non-Responder".

11.6 MINI-MENTAL STATE EXAMINATION (MMSE)

Mini-Mental State Examination (MMSE), will be completed at screening to evaluate the subject for cognitive abilities necessary for study participation.

The MMSE questionnaire, 30 items test, each scored 0 or 1, is a widely used test of cognitive function among the elderly.

To ensure precision, the EDC system calculated scores (MMS104, MMS113) will not be used in any analyses, summary tables or listings. Instead, the SAS® algorithm calculated scores (MMS104Derived, MMS112Derived) will be used. Note that no total score adjustment will be made for any potentially missing items.

The total MMSE can range from 0 to 30. The below identifies the MMSE items:

Subcategory for Question	Parameter Code	Parameter	Comment
ORIENTATION TO TIME	MMS101A	MMSE: What Is the Year	
ORIENTATION TO TIME	MMS101B	MMSE: What Is the Season	
ORIENTATION TO TIME	MMS101C	MMSE: What Is the Month of Year	
ORIENTATION TO TIME	MMS101D	MMSE: What Is the Day of Week	
ORIENTATION TO TIME	MMS101E	MMSE: What Is the Date	
ORIENTATION TO PLACE	MMS102A	MMSE: What Is the State	
ORIENTATION TO PLACE	MMS102B	MMSE: What Is the County	
ORIENTATION TO PLACE	MMS102C	MMSE: What Is the City/Town	
ORIENTATION TO PLACE	MMS102D	MMSE: What Is the Building	
ORIENTATION TO PLACE	MMS102E	MMSE: What Is the Floor	
REGISTRATION	MMS103A	MMSE: Repeat Word 1	
REGISTRATION	MMS103B	MMSE: Repeat Word 2	
REGISTRATION	MMS103C	MMSE: Repeat Word 3	
ATTENTION AND CALCULATION	MMS104	MMSE: Attention and Calculation Subtotal	
ATTENTION AND CALCULATION	MMS104AA	MMSE: What is 100 Take Away 7	Attention and Calculation: Option 1
ATTENTION AND CALCULATION	MMS104AB	MMSE: Keep Subtracting 7 Step 2	
ATTENTION AND CALCULATION	MMS104AC	MMSE: Keep Subtracting 7 Step 3	
ATTENTION AND CALCULATION	MMS104AD	MMSE: Keep Subtracting 7 Step 4	
ATTENTION AND CALCULATION	MMS104AE	MMSE: Keep Subtracting 7 Step 5	
ATTENTION AND CALCULATION	MMS104BA	MMSE: Spell Backward Letter 1	

Subcategory for Question	Parameter Code	Parameter	Comment
ATTENTION AND CALCULATION	MMS104BB	MMSE: Spell Backward Letter 2	Attention and Calculation: Option 2
ATTENTION AND CALCULATION	MMS104BC	MMSE: Spell Backward Letter 3	
ATTENTION AND CALCULATION	MMS104BD	MMSE: Spell Backward Letter 4	
ATTENTION AND CALCULATION	MMS104BE	MMSE: Spell Backward Letter 5	
ATTENTION AND CALCULATION	MMS104Derived	Attention and Calculation Subtotal	
RECALL	MMS105A	MMSE: Recall Word 1	
RECALL	MMS105B	MMSE: Recall Word 2	
RECALL	MMS105C	MMSE: Recall Word 3	
NAMING	MMS106A	MMSE: Naming Object 1	
NAMING	MMS106B	MMSE: Naming Object 2	
REPETITION	MMS107	MMSE: Repeat What I Say	
COMPREHENSION	MMS108A	MMSE: Take in Right Hand	
COMPREHENSION	MMS108B	MMSE: Fold in Half	
COMPREHENSION	MMS108C	MMSE: Put on Floor (or Table)	
READING	MMS109	MMSE: Read This and Do What It Says	
WRITING	MMS110	MMSE: Write a Sentence	
DRAWING/COPYING	MMS111	MMSE: Copy This Design	
MMSE	MMS112	MMSE: Total Score	
TOTAL MMSE	MMS112Derived	Total MMSE Score	
LEVEL OF CONSCIOUSNESS	MMS113	MMSE: Level of Consciousness	Text Description

11.7 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Two versions of C-SSRS questionnaires were used in the study as described below:

- **C-SSRS-Baseline/Screening Version**

  The Columbia-Suicide Severity Rating Scale Screening/Baseline Version (C-SSRS-BL) was taken at screening. List of questionnaire items is provided below:

Subcategory for Question	Question Short Name	Question Name*
SUICIDAL IDEATION	CSS0401A	CSS04-Wish to be Dead-Life
SUICIDAL IDEATION	CSS0401B	CSS04-Wish to be Dead-P_M
SUICIDAL IDEATION	CSS0401C	CSS04-Wish to be Dead, Describe
SUICIDAL IDEATION	CSS0402A	CSS04-Non-Spec Suicid Thought-Life
SUICIDAL IDEATION	CSS0402B	CSS04-Non-Spec Suicid Thought-P_M
SUICIDAL IDEATION	CSS0402C	CSS04-Non-Spec Suicid Thought, Describe
SUICIDAL IDEATION	CSS0403A	CSS04-Idea, No Intent, No Plan-Life
SUICIDAL IDEATION	CSS0403B	CSS04-Idea, No Intent, No Plan-P_M
SUICIDAL IDEATION	CSS0403C	CSS04-Idea, No Intent, No Plan, Describe
SUICIDAL IDEATION	CSS0404A	CSS04-Idea, Intent, No Plan-Life
SUICIDAL IDEATION	CSS0404B	CSS04-Idea, Intent, No Plan-P_M
SUICIDAL IDEATION	CSS0404C	CSS04-Idea, Intent, No Plan, Describe
SUICIDAL IDEATION	CSS0405A	CSS04-Idea, Plan, Intent-Life
SUICIDAL IDEATION	CSS0405B	CSS04-Idea, Plan, Intent-P_M
INTENSITY OF IDEATION	CSS0406A	CSS04-Most Severe Idea-Life
INTENSITY OF IDEATION	CSS0406B	CSS04-Most Severe Idea, Desc-Life
INTENSITY OF IDEATION	CSS0406C	CSS04-Most Severe Idea-P_M
INTENSITY OF IDEATION	CSS0406D	CSS04-Most Severe Idea, Desc-P_M

Subcategory for Question	Question Short Name	Question Name*
INTENSITY OF IDEATION	CSS0407A	CSS04-Most Severe Idea, Frequency-Life
INTENSITY OF IDEATION	CSS0407B	CSS04-Most Severe Idea, Frequency-P_M
INTENSITY OF IDEATION	CSS0408A	CSS04-Most Severe Idea, Duration-Life
INTENSITY OF IDEATION	CSS0408B	CSS04-Most Severe Idea, Duration-P_M
INTENSITY OF IDEATION	CSS0409A	CSS04-Most Severe Idea, Control-Life
INTENSITY OF IDEATION	CSS0409B	CSS04-Most Severe Idea, Control-P_M
INTENSITY OF IDEATION	CSS0410A	CSS04-Most Severe Idea, Deterrents-Life
INTENSITY OF IDEATION	CSS0410B	CSS04-Most Severe Idea, Deterrents-P_M
INTENSITY OF IDEATION	CSS0411A	CSS04-Most Severe Idea, Reasons-Life
INTENSITY OF IDEATION	CSS0411B	CSS04-Most Severe Idea, Reasons-P_M
SUICIDAL BEHAVIOR	CSS0412A	CSS04-Actual Attempt-Life
SUICIDAL BEHAVIOR	CSS0412B	CSS04-Actual Attempt-P_Y
SUICIDAL BEHAVIOR	CSS0413A	CSS04-Number of Actual Attempts-Life
SUICIDAL BEHAVIOR	CSS0413B	CSS04-Number of Actual Attempts-P_Y
SUICIDAL BEHAVIOR	CSS0414A	CSS04-Non-suicidal Self-injur Behav-Life
SUICIDAL BEHAVIOR	CSS0414B	CSS04-Non-suicidal Self-injur Behav-P_Y
SUICIDAL BEHAVIOR	CSS0415A	CSS04-Interrupted Attempt-Life
SUICIDAL BEHAVIOR	CSS0415B	CSS04-Interrupted Attempt-P_Y
SUICIDAL BEHAVIOR	CSS0416A	CSS04-Number of Interrupt Attempts-Life
SUICIDAL BEHAVIOR	CSS0416B	CSS04-Number of Interrupt Attempts-P_Y
SUICIDAL BEHAVIOR	CSS0417A	CSS04-Aborted Attempt-Life
SUICIDAL BEHAVIOR	CSS0417B	CSS04-Aborted Attempt-P_Y
SUICIDAL BEHAVIOR	CSS0418A	CSS04-Number of Aborted Attempts-Life
SUICIDAL BEHAVIOR	CSS0418B	CSS04-Number of Aborted Attempts-P_Y
SUICIDAL BEHAVIOR	CSS0419A	CSS04-Preparatory Acts/Behavior-Life
SUICIDAL BEHAVIOR	CSS0419B	CSS04-Preparatory Acts/Behavior-P_Y
SUICIDAL BEHAVIOR	CSS0419C	CSS04-Preparatory Acts/Behav, Descr
SUICIDAL BEHAVIOR	CSS0420A	CSS04-Suicidal Behavior-Life
SUICIDAL BEHAVIOR	CSS0420B	CSS04-Suicidal Behavior-P_Y

*** Question name ends with "-Life" relates to lifetime interval, those end with "-P_M" or to "-P_Y" relate to past 6 months interval**

- **C-SSRS-SLV (Since Last Visit Version)**

  The Columbia-Suicide Severity Rating Scale Since Last Visit (C-SSRS-SLV) was assessed at baseline and at each schedule visit afterwards (except at end of week 4 visit). List of questionnaire items is provided below:

Subcategory for Question	Question Short Name	Question Name
SUICIDAL IDEATION	CSS0201	CSS02-Wish to be Dead
SUICIDAL IDEATION	CSS0201A	CSS02-Wish to be Dead, Describe
SUICIDAL IDEATION	CSS0202	CSS02-Non-Specific Suicidal Thought
SUICIDAL IDEATION	CSS0202A	CSS02-Non-Specific Suicid Thought, Descr
SUICIDAL IDEATION	CSS0203	CSS02-Suicidal Ideation-No Intent
SUICIDAL IDEATION	CSS0204	CSS02-Ideation With Intent, No Plan
SUICIDAL IDEATION	CSS0205	CSS02-Ideation With Plan/Intent
INTENSITY OF IDEATION	CSS0206	CSS02-Most Severe Ideation
INTENSITY OF IDEATION	CSS0206A	CSS02-Most Severe Ideation, Description
INTENSITY OF IDEATION	CSS0207	CSS02-Most Severe Ideation, Frequency
INTENSITY OF IDEATION	CSS0208	CSS02-Most Severe Ideation, Duration
INTENSITY OF IDEATION	CSS0209	CSS02-Most Severe Ideation, Control
INTENSITY OF IDEATION	CSS0210	CSS02-Most Severe Ideation, Deterrents
INTENSITY OF IDEATION	CSS0211	CSS02-Most Severe Ideation, Reasons
SUICIDAL BEHAVIOR	CSS0212	CSS02-Actual Attempt
SUICIDAL BEHAVIOR	CSS0213	CSS02-Number of Actual Attempts
SUICIDAL BEHAVIOR	CSS0214	CSS02-Non-suicidal Self-injurious Behav
SUICIDAL BEHAVIOR	CSS0215	CSS02-Interrupted Attempt
SUICIDAL BEHAVIOR	CSS0216	CSS02-Number of Interrupted Attempts
SUICIDAL BEHAVIOR	CSS0217	CSS02-Aborted Attempt
SUICIDAL BEHAVIOR	CSS0218	CSS02-Number of Aborted Attempts
SUICIDAL BEHAVIOR	CSS0219	CSS02-Preparatory Acts/Behavior
SUICIDAL BEHAVIOR	CSS0220	CSS02-Suicidal Behavior
SUICIDAL BEHAVIOR	CSS0221	CSS02-Suicide
SUICIDAL BEHAVIOR	CSS0222C	CSS02-Most Lethal Attempt Potential

- **Definition of "Suicidal behavior", "Suicidal Ideation" and "Suicidal Behavior or Ideation" at Baseline**

  The Columbia-Suicide Severity Rating Scale Screening/Baseline Version (C-SSRS-BL) was taken at screening. The Columbia-Suicide Severity Rating Scale Since Last visit Version (C-SSRS-SLV) was taken at baseline visit which was scheduled to be performed before first study drug administration.

  Any "Yes" answer to the suicidal behavior items at screening or at baseline visit identifies a subject as with "Suicidal Behavior at Baseline".

  Similarly, any "Yes" to its suicidal ideation items at screening or at baseline identifies a subject as with "Suicidal Ideation at Baseline".

  A subject identified with either "Suicidal Behavior at Baseline" or with "Suicidal Ideation at Baseline" was also classified as with "Suicidal Behavior or Ideation" at Baseline.

- **Definition of "Suicidal behavior", "Suicidal Ideation" and "Suicidal Behavior or Ideation" Post Baseline**

  The Columbia-Suicide Severity Rating Scale Since Last Visit Version (C-SSRS-SLV) was taken at each visit post baseline.

  Any "Yes" answer to its suicidal behavior items at any post baseline visit identifies a subject as with "Suicidal Behavior Post Baseline".

  Similarly, any "Yes" answer to its suicidal ideation items identifies a subject as with "Suicidal Ideation Post Baseline".

  A subject identified with either "Suicidal Behavior Post Baseline" or with "Suicidal Ideation Post Baseline" will also be classified as with "Suicidal Behavior or Ideation Post Baseline".

11.8 PARKINSON'S DISEASE QUALITY OF LIFE QUESTIONNAIRE (PDQ39)

This is a PD specific health-related quality of life scale that will be performed at baseline visit and at end of week 12/Treatment Termination (visit 6). There are 39 questions in the PDQ-39, with 8 discrete scales:

- Mobility (10 items)
- Activities of daily living (6 items)
- Emotional well-being (6 items)
- Stigma (4 items)
- Social support (3 items)
- Cognitions (4 items)
- Communication (3 items)
- Bodily discomfort (3 items)

Subjects are asked to think about their health and general well-being and to consider how often in the last month they have experienced certain events (e.g. difficulty walking 100 yards). Subjects are asked to indicate the frequency of each event by selecting one of 5 options (Likert Scale):

- 0 = Never
- 1 = Occasionally
- 2 = Sometimes
- 3 = Often
- 4 = Always

List of PDQ39 questionnaire (QSCAT= PDQUALIF in QS STDM domain**)** items are listed in the below table along with their 8 dimensions:

PDQ-39 Subscales	Question Short Name	Question Name
Mobility	PDQ3901	Had difficulty doing leisure activities?
Mobility	PDQ3902	Had difficulty looking after your home?
Mobility	PDQ3903	Had difficulty carrying shopping bags?

PDQ-39 Subscales	Question Short Name	Question Name
Mobility	PDQ3904	Had problems walking half a mile?
Mobility	PDQ3905	Had problems walking 100 yards?
Mobility	PDQ3906	Had problems getting around the house?
Mobility	PDQ3907	Had difficulty getting around in public?
Mobility	PDQ3908	Needed someone else to accompany you?
Mobility	PDQ3909	Felt frightened about falling in public?
Mobility	PDQ3910	Been confined to the house more?
Activities of daily living (ADL)	PDQ3911	Had difficulty washing yourself?
Activities of daily living (ADL)	PDQ3912	Had difficulty dressing yourself?
Activities of daily living (ADL)	PDQ3913	Had problems doing up your shoe laces?
Activities of daily living (ADL)	PDQ3914	Had problems writing clearly?
Activities of daily living (ADL)	PDQ3915	Had difficulty cutting up your food?
Activities of daily living (ADL)	PDQ3916	Difficulty holding drink without spill?
Emotional well being	PDQ3917	Felt depressed?
Emotional well being	PDQ3918	Felt isolated and lonely?
Emotional well being	PDQ3919	Felt weepy or tearful?
Emotional well being	PDQ3920	Felt angry or bitter?
Emotional well being	PDQ3921	Felt anxious?
Emotional well being	PDQ3922	Felt worried about your future?
Stigma	PDQ3923	Felt you had to conceal your PD?
Stigma	PDQ3924	Avoided situations - eating or drinking?
Stigma	PDQ3925	Felt embarrassed in public due to PD?
Stigma	PDQ3926	Felt worried by other people's reaction?
Social support	PDQ3927	Problems with personal relationships?
Social support	PDQ3928	Lacked support from spouse or partner?
Social support	PDQ3929	Lacked support from family or friends?
Cognitive impairment (Cognitions)	PDQ3930	Unexpectedly fallen asleep during day?
Cognitive impairment (Cognitions)	PDQ3931	Had problems with your concentration?
Cognitive impairment (Cognitions)	PDQ3932	Felt your memory was bad?
Cognitive impairment (Cognitions)	PDQ3933	Distressing dreams or hallucinations?
Communication	PDQ3934	Had difficulty with your speech?
Communication	PDQ3935	Felt unable to communicate with people?
Communication	PDQ3936	Felt ignored by people?
Bodily discomfort	PDQ3937	Had painful muscle cramps or spasms?
Bodily discomfort	PDQ3938	Had aches and pains in joints or body?
Bodily discomfort	PDQ3939	Felt unpleasantly hot or cold?

Derivation of Scores:

- Each dimension is calculated as a scale from 0 to 100, where 0 is indicative of no problem at all and 100 is the maximum level of problem.
- If the response to a question is missing, no scale score is calculated for that individual for that dimension. This will preclude calculation of the PDQ39 single index score from the eight domains.
- Mobility: [(sum of scores of questions 1 to 10) / (4 x 10)] x 100

- Activities of daily living: [(sum of scores of questions 11 to 16) / (4 x 6)] x100
- Emotional wellbeing: [(sum of scores of questions 17 to 22) / (4 x 6)]x 100
- Stigma: [(sum of scores of questions 23 to 26) / (4 x 4)] x 100
- Social support: [(sum scores of questions 27 to 29) / (4 x 3)] x 100

  note: if respondents indicate that they do not have a spouse or partner on question 28 then social support can be calculated as follows:
  Social support = [(scores of questions 27+29) / (4 x 2)] x 100
- Cognitions: [(sum of scores of questions 30 to 33) / (4 x 4)] x 100
- Communication: [(sum of scores of questions 34 to 36) / (4 x 3)] x 100
- Bodily discomfort: [(sum scores of questions 37 to 39) / (4 x 3)] x 100
- Total Score of PDQ39: Sum of dimension scores / 8

11.9 EPWORTH SLEEPINESS SCALE (ESS)

The ESS is a self-administered questionnaire with 8 questions taken at baseline and at end of Weeks 5, 8 and 12. It provides a measure of a person's general level of daytime sleepiness, or their average sleep propensity in daily life. The ESS asks people to rate, on a 4-point scale (0 – 3), their usual chances of dozing off or falling asleep in 8 different situations or activities that most people engage in as part of their daily lives, although not necessarily every day.

The total ESS score is the sum of 8 item-scores and can range between 0 and 24. The total ESS score is the sum of 8 item-scores. If one or more item-scores are missing, that ESS is invalid as it is not feasible to interpolate missing item-scores.

List of ESS questionnaire items are listed in the below table:

Question Name	Question Short Name
ESS01-Sitting and Reading	ESS0101
ESS01-Watching TV	ESS0102
ESS01-Sitting Inactive in a Public Place	ESS0103
ESS01-Passenger for Hour Without Break	ESS0104
ESS01-Lying Down to Rest In Afternoon	ESS0105
ESS01-Sitting and Talking to Someone	ESS0106
ESS01-Sitting Quietly After Lunch	ESS0107
ESS01-In Car Stopped Few Minutes Traffic	ESS0108

Derivation of Scores:

- The total ESS score is the sum of 8 item-scores and can range between 0 and 24.
- ESS score >10: A subject with ESS score>10 at any time post baseline will be classified as having "Post-Baseline ESS>10". Otherwise (precluding missing values), the subject will be classified as "Otherwise".

- Shift from Baseline in ESS Score: A subject with baseline ESS≤10 and at least one ESS>10 post baseline will be classified as "ESS≤10→ESS>10". Otherwise (precluding missing values) subject will be classified as "Otherwise".

11.10 ORTHOSTATIC HYPOTENSION SYMPTOMS ASSESSMENT (OHSA) QUESTION 1

OHSA question 1 ("Dizziness, lightheadedness, feeling faint or feeling as though you might pass out") will be completed only by subjects experiencing orthostatic hypotension.

The OHSA Q1 item value ranges from 0 to 10 where 0=None and 10=Worst Possible that best rates how severe were the symptoms from low blood pressure have been on average over the past week.

List of OHSA questionnaire item and derived items are listed in the below table:

Category of Question	Question Short Name	Question Name
OHSA	OHSA101	OHSA Question 1. Dizziness
OHSA	OHSADerived1	OHSA Q1 Score>0
OHSA	OHSADerived2	OHSA Q1 Post Baseline Maximal Score

Derivation of Scores:

- **OHSADerived1:** Each Q1 item value either taken before or after first study dose will be classified as =0 indicative of no clinical symptoms or >0 with clinical symptoms at any level.
- **OHSADerived2:** The post baseline OHSA Maximal Score will be derived on a by subject basis.

11.11 IMPULSIVE-COMPULSIVE DISORDERS IN PARKINSON'S DISEASE (QUIP-RATING SCALE)

The questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, (QUIP-Rating Scale) will be collected at baseline visit and at end of weeks 3, 5, 8, 12/Treatment Termination visit and end of week 14 (visits 3, 4, 5, 6 and 7). The answers for all questions are based on current behaviors and behaviors occurred in the past 4 weeks.

The QUIP-RS consists of an instruction sheet and a second sheet with four questions which have to be answered for each 7 disorders on a 5-point Likert scale where 0=Never, 1=Rarely, 2=Sometimes, 3=Often and 4=Very Often.

The subcategories of the QUIP-RS originally provided in the SDTM SAS® database were modified in line with QUIP-RATING SCALE [Version 1.0 (7/01/09) Copyright© University of Pennsylvania 2009].

List of QUIP-RS questionnaire subscales and items are listed in the below table along with their modified 6 dimensions (hobbyism and punding are combined):

QUIP-RS Dimension	Question Short Name	Question Short Name
I. GAMBLING	QUI101A	Think about:Gambling?
I. GAMBLING	QUI102A	Excessive:Gambling?
I. GAMBLING	QUI103A	Controlling:Gambling?
I. GAMBLING	QUI104A	Engage:Gambling?
II. SEX	QUI101B	Think about:Sex?
II. SEX	QUI102B	Excessive:Sex?
II. SEX	QUI103B	Controlling:Sex?
II. SEX	QUI104B	Engage:Sex?
III. BUYING	QUI101C	Think about:Buying?
III. BUYING	QUI102C	Excessive:Buying?
III. BUYING	QUI103C	Controlling:Buying?
III. BUYING	QUI104C	Engage:Buying?
IV. EATING	QUI101D	Think about:Eating?
IV. EATING	QUI102D	Excessive:Eating?
IV. EATING	QUI103D	Controlling:Eating?
IV. EATING	QUI104D	Engage:Eating?
V. HOBBYISM-PUNDING	QUI101E	Think about:Performing tasks or hobbies?
V. HOBBYISM-PUNDING	QUI102E	Excessive:Performing tasks or hobbies?
V. HOBBYISM-PUNDING	QUI103E	Controlling:Performing tasks or hobbies?
V. HOBBYISM-PUNDING	QUI104E	Engage:Performing tasks or hobbies?
V. HOBBYISM-PUNDING	QUI101F	Think about:Repeating simple activities?
V. HOBBYISM-PUNDING	QUI102F	Excessive:Repeating simple activities?
V. HOBBYISM-PUNDING	QUI103F	Controlling:Repeating simple activities?
V. HOBBYISM-PUNDING	QUI104F	Engage:Repeating simple activities?
VI. MEDICATIONS	QUI101G	Think about:Taking your PD medications?
VI. MEDICATIONS	QUI102G	Excessive:Taking your PD medications?
VI. MEDICATIONS	QUI103G	Controlling:Taking your PD medications?
VI. MEDICATIONS	QUI104G	Engage:Taking your PD medications?

Derivation of Scores:

- Total QUIP-RS Score: Sum of 28 items (ranges from 0-112). If the response to a question is missing, no Total QUIP-RS Score will be calculated.
- The total scores for each dimension will be calculated as the sum of corresponding items. If the response to a question is missing, no scale score is calculated for that individual for that dimension
- Gambling: 4 items ranges 0-16.
- Sex: 4 items ranges 0-16.
- Buying: 4 items ranges 0-16.
- Eating: 4 items ranges 0-16.
- Hobbyism-Punding: 8 items ranges 0-32.

- Medications: 4 items ranges 0-16.
- ICD Score: Sum of gambling, sex, buying and eating, ranges 0-60

11.12 HEALTH-RELATED QUALITY OF LIFE (HRQOL) SF-12V2

The HRQOL SF-12v2 questionnaire assesses the physical and mental health of the patient using 12 questions related to eight aspects of health (physical and social functioning, role limitation due to physical limitation, vitality, role limitation due to emotional problems, bodily pain, mental and general health). This questionnaire will be filled in on the baseline visit and at end of week 12/Treatment.

Originally eCRF items provided in SDTM database which were used by data management to derive the norm based scores are listed below:

Question Short Name	Question Name
SF12101	SF12: Would You Say Your Health Is
SF12102A	SF12: Typical day : Moderate activities
SF12102B	SF12: Typical day : Climbing stairs
SF12103A	SF12: Physical health : Accomplish less
SF12103B	SF12: Physical health : Limited
SF12104A	SF12: Emotional prob : Accomplish less
SF12104B	SF12: Emotional prob : Less carefully
SF12105	SF12: How much did pain interfere
SF12106A	SF12: Past4wks : Felt calm and peaceful?
SF12106B	SF12: Past4wks : Have a lot of energy?
SF12106C	SF12: Past4wks : Felt Downhearted?
SF12107	SF12: Interfered with social activities

List of the norm based derived items (with the addition of '_Derived' to each) provided in SDTM database are listed below:

Question Short Name	Question Name
BP_Derived	Bodily Pain 0-100 Score
BP_NBS_Derived	Bodily Pain Norm-Based Score
GH_Derived	General Health 0-100 Score
GH_NBS_Derived	General Health Norm-Based Score
MCS_Derived	Mental Component Score
MH_Derived	Mental Health 0-100 Score
MH_NBS_Derived	Mental Health Norm-Based Score
PCS_Derived	Physical Component Score
PF_Derived	Physical Functioning 0-100 Score
PF_NBS_Derived	Physical Functioning Norm-Based Score
RE_Derived	Role Emotional 0-100 Score
RE_NBS_Derived	Role Emotional Norm-Based Score
RP_Derived	Role Physical 0-100 Score
RP_NBS_Derived	Role Physical Norm-Based Score
SF_Derived	Social Functioning 0-100 Score

Question Short Name	Question Name
SF6D_R2_Derived	SF-6D_R2 (Utility Index Release 2) Score
SF_NBS_Derived	Social Functioning Norm-Based Score
VT_Derived	Vitality 0-100 Score
VT_NBS_Derived	Vitality Norm-Based Score

Scores to be used in exploratory analyses:

- Mental Component Summary Score (MCS_Derived).
- Physical Component Summary Score (PCS_Derived).

12 PLANNED SUBGROUPS ANALYSES

This study was not powered for subgroup analyses and therefore all of the below proposed analyses will be conducted in an exploratory manner.

As the study was not powered for subgroups analyses, the below proposed subgroups assessments will be limited to the descriptive presentation of the primary endpoint treatment effect magnitude and to the overall incidence of TEAEs and serious TEAEs. Other post-hoc assessments might also be reported in the CSR based on clinical relevance.

Subgroups descriptive statistical assessment for the primary efficacy endpoint is described in more detail as part of the sensitivity analyses planned for the primary endpoint is described in Descriptive Subgroups Analysis.

The descriptive assessment of TEAEs and serious TEAEs will be provided in summary tables displaying the incidence (no. of subjects and percentages) and frequency (no. of events) of the observed TEAEs.

Subgroups analyses will be conducted according to the below factors:

- Gender.
- Study population (North Americans or Non North Americans)
- Age (<=Median ITT Age, > Median ITT Age)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Other)

13 EFFICACY ENDPOINTS

13.1 PRIMARY EFFICACY ENDPOINT

Change from Baseline (Derived) to End of Week 12 Visit in the total UPDRS (UPDRS part II+III) score.

13.2 SECONDARY EFFICACY ENDPOINTS

Secondary efficacy endpoints will be analyzed in the order of hierarchy testing (See Significance Level and Multiplicity Adjustment):

1. Change from Baseline (Derived) to End of Week 12 Visit in Epworth Sleepiness Scale (ESS) score.
2. Change from Baseline (Derived) to End of Week 12 Visit in Motor UPDRS (part III) score.
3. Change from Baseline (Derived) to End of Week 12 Visit in ADL UPDRS (part II) score.
4. Change from Baseline (Derived) to End of Week 12 in ADL subscale score of PDQ39.
5. Change from Baseline (Derived) to End of Week 12 Visit in Total PDQ39 score.

13.3 EXPLORATORY ENDPOINTS

Exploratory endpoints and pre-defined analyses are displayed in Exploratory Endpoints and Analyses (P2B001 Vs. Components).

13.4 ADDITIONAL EXPLORATORY ENDPOINTS

Additional exploratory endpoints and pre-defined analyses are displayed in Additional Exploratory Endpoints and Analyses (P2B001 VS. Prami-ER).

14 SIGNIFICANCE LEVEL AND MULTIPLICITY ADJUSTMENT

One (1) primary endpoint and five (5) secondary endpoints are pre-defined for this study. The overall significance level for this study will be 5% using two-tailed tests utilizing the hierarchical gate keeping method to control the overall Type I error rate. A total of 12 contrasts are pre-planned for the primary and secondary endpoints altogether. Testing will be performed according to the below order and rules:

Order	Contrasts to be Tested in the Order Listed
1st	**Primary Endpoint**: Change from Baseline (Derived) to End of Week 12 Visit in the **Total UPDRS** (UPDRS part II+III) score: P2B001 vs. pramipexole 0.6 mg (PPX) and P2B001 vs. rasagiline (RAS) contrasts. The primary endpoint will be considered as met only if both contrasts favor P2B001 at a two-tailed significance level of 5% each.
2nd	**1st Secondary Endpoint**: Change from Baseline (Derived) to Week 12 Visit in the **Total ESS** Score: P2B001 vs. Pramipexole ER (PramiER) contrast. This endpoint will formally be tested only if the primary endpoint (two contrasts) is met. This endpoint will be considered as met if the analysis favors P2B001 at a two-tailed significance level of 5%.
3rd	**2nd Secondary Endpoint:** Change from Baseline (Derived) to End of Week 12 Visit in **Motor UPDRS** score (UPDRS part III): P2B001 vs. PPX and P2B001 vs. RAS contrasts. This endpoint will formally be tested only if the primary endpoint (two contrasts) and the 1st secondary endpoint (one contrast) and are all met. This endpoint will be considered as met only if both contrasts favor P2B001 at a two-tailed significance level of 5% each
4th	**3rd Secondary Endpoint**: Change from Baseline (Derived) to End of Week 12 Visit in **ADL UPDRS** score (UPDRS part II): P2B001 vs. PPX and P2B001 vs. RAS contrasts. This endpoint will formally be tested only if the primary endpoint (two contrasts), the 1st secondary endpoint (one contrast) and the 2nd secondary endpoint (two contrasts) are all met. This endpoint will be considered as met only if both contrasts favor P2B001 at a two-tailed significance level of 5% each.
5th	**4th Secondary Endpoint**: Change from Baseline (Derived) to Week 12 Visit in the **ADL subscale score of PDQ39**: P2B001 vs. PramiER contrast. This endpoint will formally be tested only if the primary endpoint (two contrasts), the 1st secondary endpoint (one contrast), the 2nd secondary endpoint (two contrasts) and the 3rd secondary endpoint (two contracts) are all met. This endpoint will be considered as met if the analysis favors P2B001 at a two-tailed significance level of 5%.

6th	**4th Secondary Endpoint**: Change from Baseline (Derived) to Week 12 Visit in the **ADL subscale score of PDQ39**: P2B001 vs. PPX and P2B001 vs. RAS contrasts. This endpoint will formally be tested only if the primary endpoint (two contrasts), the 1st secondary endpoint (one contrast), the 2nd secondary endpoint (two contrasts), the 3rd secondary endpoint (two contrasts) and the 4th secondary endpoint (P2B001 vs. PramiER contrast) are all met. This endpoint will be considered as met if both contrasts favor P2B001 at a two-tailed significance level of 5% each.
7th	**5th Secondary Endpoint**: Change from Baseline (Derived) to End of Week 12 Visit in the **Total PDQ39** score: P2B001 vs. PPX and P2B001 vs. RAS contrasts. This endpoint will formally be tested only if the primary endpoint (two contrasts), the 1st secondary endpoint (one contrast), the 2nd secondary endpoint (two contrasts), the 3rd secondary endpoint (two contrasts) and the 4th secondary endpoint (three contrasts) are all met. This endpoint will be considered as met only if both contrasts favor P2B001 at a two-tailed significance level of 5% each.

Nominal p-values will be reported in the CSR in the case of failure to reach the above defined statistical significance.

15 ESTIMANDS AND MULTIPLE IMPUTATIONS

15.1 PRIMARY ESTIMAND (MAIN SUPPORTIVE ESTIMAND)

The **Primary Estimand** will be the efficacy Estimand and is based on efficacy assumption (de-jure).

The **Primary Estimand** construction elements are:

1. Treatment of Interest: Will be the initially randomized treatment taken **as planned**: P2B001 vs. pramipexole 0.6mg and P2B001 vs. rasagiline.
2. Population: Subjects with Early Parkinson's Disease that were randomized to the study.
3. Variable of interest: change from Baseline (Derived) to End of Week 12 in the total UPDRS score**.**
4. Inter-current events: Subjects that ETT for whatever reason, or, for whom treatment with rescue therapy was initiated during the double-blind treatment period.
5. Population-level summary: The between groups (P2B001 vs. pramipexole 0.6mg and P2B001 vs. rasagiline) difference in the change from Baseline (Derived) to End of Week 12 in the total UPDRS score.

The treatment effect under the **Primary Estimand** will be attributed to subjects with Early Parkinson's Disease that were randomized to the study, assuming that subjects treated with P2B001 or with pramipexole 0.6mg ceased to have the additional benefit over rasagiline (its treatment effect is expected to be less prominent among all 4 study arms; see Per-Protocol Sample Size and Power Considerations) following the use of rescue therapy. Treatment effect for subjects ETT due to whatever reason receiving no rescue therapy will be assumed as if those subjects did not discontinue and had full adherence to treatment. The incorporation of the **Primary Estimand** implies that observations collected post rescue therapy initiation, as well as post ETT for whatever reason will not be included in the analysis and will be multiply imputed as described below:

1. Missing values following rescue therapy uptake will multiply be imputed using rasagiline (RAS 0.75) based imputation as control reference assuming missing not at random (MNAR).
2. Missing values following ETT due to whatever reason for subjects receiving no rescue therapy will multiply be imputed under MAR assumption.

The analysis related to the **Primary Estimand** will use the m**ITT Analysis Set** and will be considered as the **Main Supportive Estimand** for the principal analysis of the primary endpoint.

15.2 SECONDARY ESTIMAND (ADDITIONAL SUPPORTIVE ESTIMAND)

The **Secondary Estimand** will be the effectiveness Estimand and is based on the effectiveness assumption (de-facto).

The **Secondary Estimand** construction elements are:

1. Treatment of Interest: Will be the initially randomized treatment **as actually taken**: P2B001 vs. pramipexole 0.6mg and P2B001 vs. rasagiline.
2. Population: Subjects with Early Parkinson's Disease that were randomized to the study.
3. Variable of interest: change from Baseline (Derived) to End of Week 12 in the total UPDRS score**.**
4. Inter-current events: Subjects that ETT due to treatment related reason, ETT due to non-treatment related reason, or, for whom treatment with rescue therapy was initiated during the double-blind treatment period.
5. Population-level summary: The between groups (P2B001 vs. pramipexole 0.6mg and P2B001 vs. rasagiline) difference in the change from Baseline (Derived) to End of Week 12 in the total UPDRS score.

The treatment effect under the **Secondary Estimand** will be attributed to subjects with Early Parkinson's Disease that were randomized to the study, assuming that subjects treated with P2B001 or with pramipexole 0.6mg ceased to have the additional benefit over rasagiline (its treatment effect is expected to be less prominent among all 4 study arms; see Per-Protocol Sample Size and Power Considerations) following the use of rescue therapy or following ETT due to treatment related reasons. Treatment effect for subjects ETT due to non-treatment related reasons receiving no rescue therapy will be assumed as if those subjects did not discontinue and had full adherence to treatment.

The incorporation of the **Secondary Estimand** implies the following:

3. Observations collected post rescue therapy initiation and/or post ETT will not be included in the analysis and will be multiply imputed as described below.
4. Missing values following ETT due to treatment related reasons and/or following rescue therapy uptake will multiply be imputed using rasagiline (RAS 0.75) based imputation as control reference assuming missing not at random (MNAR).
5. Missing values following ETT due to non-treatment related reasons for subjects receiving no rescue therapy will multiply be imputed under MAR assumption.

The analysis related to the **Secondary Estimand** for the **mITT Analysis Set** will be considered as the **Additional Supportive Estimand** for the principal analysis of the primary endpoint.

15.3 TERTIARY ESTIMAND (SENSITIVITY ESTIMAND)

The **Tertiary Estimand** will have the same construction elements as described for the **Primary Estimand** with the exception that all data collected in database, regardless if collected following of rescue therapy initiation and/or ETT for whatever reason will be included in the calculation of the population level summary. Any post-baseline missing data will be multiply imputed under MNAR, altogether reflecting the worst-case scenario.

The analysis related to the **Tertiary Estimand** for the **mITT Analysis Set** will be considered as a **Sensitivity Estimand** to the **Main Supportive Estimand**.

15.4 MULTIPLE IMPUTATIONS

General comment: In the case of obtaining an error message due to the choice of the below specified seed value, the **MINMAXITER=1000 option will be used and the** last two digits of the specified seed will be added to the pre-specified value until error resolution.

15.4.1 Multiple Imputations for the Primary Estimand

1. Step 1: At the initial stage, a dataset (named "**MIin1stEst**") will be constructed, including, per ITT subject (in one dataset record) the following: treatment arm to which subject was randomized to (TRTP), Pooled Country/Geographical Region (CGR1), initiation date of rescue therapy, treatment termination reason, date of last P2B001/Placebo treatment and Total UPDRS as measured at Baseline (Derived), End of Week 5, End of Week 8 and End of Week 12. Observations in **MIin1stEst** collected post rescue therapy initiation, as well as post last P2B/Placebo administration date of ETT subjects for whatever reason will be set to missing values.

2. Step 2: Using the previously described "**MIin1stEst**" dataset, the Markov Chain Monte Carlo (MCMC) methodology for creating a monotone missingness pattern imputation model will be used to generate multiply imputed datasets for intermittent missing values. Treatment (TRTP) will be used in the BY statement and the Total UPDRS scores at Baseline (Derived), End o Week 5, End of Week 8 and End of Week 12 will be identified in the VAR statement. The number of imputations will be 100 and the procedure will use a seed of 1234 for this imputation step under the MAR assumption. The SAS® code for this step is provided below:

```
PROC MI DATA=MIin1stEst OUT=TMP NIMPUTE=100 seed=1234
     minimum=0 0 0 0 maximum=160 160 160 160;
     by trtp;
     VAR BL W5 W8 W12;
     MCMC CHAIN=MULTIPLE IMPUTE=MONOTONE;
run;
```

3. Step 3: For each of the 100 intermittent imputed datasets, the remaining missing data will then be imputed using the method for monotone regression missingness. Treatment (TRTP) will be used in the BY statement and the Total UPDRS scores at Baseline (Derived), End o Week 5, End of Week 8 and End of Week 12 as well as CGR1 will be identified in the VAR statement. The number of imputations will be 1 and the procedure will use a seed of 2345 for this imputation step. The SAS® code for this step is provided below:

```
PROC MI data=TMP out=TMP1 NIMPUTE=1 seed=2345
     minimum=. 0 0 0 0 maximum=. 160 160 160 160;
     by trtp;
     class cgr1;
     VAR cgr1 BL W5 W8 W12;
     monotone regression;
run;
```

4. Step 4: Scores multiply imputed in previous step under MAR following rescue therapy will then be set to missing values in all 100 imputed datasets for the purpose of MI under MNAR. Thereafter, for each of the 100 imputed datasets, multiple imputations using the method for monotone regression missingness will be performed with rasagiline (RAS 0.75) based imputation as control reference under MNAR as its treatment effect is expected to be less prominent among all 4 study arms. Total UPDRS scores at Baseline (Derived), End of Week 5, End of Week 8, and End of Week 12 as well as CGR1 will be identified in the VAR statement. The number of imputations will be 1 and the procedure will use a seed of 2345 for this imputation step. The SAS® code for this step is provided below:

```
PROC MI data=TMP1 out=MIout2ndEst NIMPUTE=1 seed=2345
     minimum=. . 0 0 0 0 maximum=. . 160 160 160 160;
     class trtp cgr1;
     VAR cgr1 BL W5 W8 W12;
     monotone regression;
     MNAR model (W5 W8 W12/modelobs=(trtp='RAS 0.75'));
     by _imputation_;
run;
```

5. Step 5: For each subject within each of the 100 imputed datasets the change from Baseline (Derived) to the End of Week 12 (CHG) will be calculated to be used in the statistical analysis of the change from baseline to Week 12 visit in the total UPDRS score employing the mITT referring to the **Primary Estimand**.

15.4.2 Multiple Imputations for the Secondary Estimand

1. Step 1: At the initial stage, a dataset (named "**MIin2ndEst**") will be constructed, including, per ITT subject (in one dataset record) the following: treatment arm to which subject was randomized to (TRTP), Pooled Country/Geographical Region (CGR1), initiation date of rescue therapy, treatment termination reason, date of last P2B001/Placebo treatment and Total UPDRS as measured at Baseline (Derived), End of Week 5, End of Week 8 and End of Week 12. Observations in **MIin2ndEst** collected post rescue therapy initiation will be set to missing values.

2. Step 2: Using the previously described "**MIin2ndEst**" dataset, the Markov Chain Monte Carlo (MCMC) methodology for creating a monotone missingness pattern imputation model will be used to generate multiply imputed datasets for intermittent missing values. Treatment (TRTP) will be used in the BY statement and the Total UPDRS scores at Baseline (Derived), End o Week 5, End of Week 8 and End of Week 12 will be identified in the VAR statement. The number of imputations will be 100 and the procedure will use a seed of 3456 for this imputation step under the MAR assumption. The SAS® code for this step is provided below:

```
PROC MI DATA=MIin2ndEst OUT=TMP NIMPUTE=100 seed=3456
     minimum=0 0 0 0 maximum=160 160 160 160;
     by trtp;
     VAR BL W5 W8 W12;
     MCMC CHAIN=MULTIPLE IMPUTE=MONOTONE;
run;
```

3. Step 3: For each of the 100 intermittent imputed datasets, the remaining missing data will then be imputed using the method for monotone regression missingness. Treatment (TRTP) will be used in the BY statement and the Total UPDRS scores at Baseline (Derived), End o Week 5, End of Week 8 and End of Week 12 as well as CGR1 will be identified in the VAR statement. The number of imputations will be 1 and the procedure will use a seed of 4567 for this imputation step. The SAS® code for this step is provided below:

```
PROC MI data=TMP out=TMP1 NIMPUTE=1 seed=4567
     minimum=. 0 0 0 0 maximum=. 160 160 160 160;
     by trtp;
     class cgr1;
     VAR cgr1 BL W5 W8 W12;
     monotone regression;
run;
```

4. Step 4: Scores multiply imputed in previous step under MAR following rescue therapy and/or following ETT due to treatment related reasons will then be set to missing values in all 100 imputed datasets for the purpose of MI under MNAR. Thereafter, for each of the 100 imputed datasets, multiple imputations using the method for monotone regression missingness will be performed with rasagiline (RAS 0.75) based imputation as control reference under MNAR as its treatment

effect is expected to be less prominent among all 4 study arms. Total UPDRS scores at Baseline (Derived), End o Week 5, End of Week 8, and End of Week 12 as well as CGR1 will be identified in the VAR statement. The number of imputations will be 1 and the procedure will use a seed of 4567 for this imputation step. The SAS® code for this step is provided below:

```
PROC MI data=TMP out=MIout2ndEst NIMPUTE=1 seed=4567
     minimum=. . 0 0 0 0 maximum=. . 160 160 160 160;
     class trtp cgr1;
     VAR cgr1 BL W5 W8 W12;
     monotone regression;
     MNAR model (W5 W8 W12/modelobs=(trtp='RAS 0.75'));
     by _imputation_;
run;
```

5. Step 5: For each subject within each of the 100 imputed datasets the change from Baseline (Derived) to the End of Week 12 (CHG) will be calculated to be used in the statistical analysis of the change from baseline to Week 12 visit in the total UPDRS score employing the mITT referring to the **Secondary Estimand**.

15.4.3 Multiple Imputations for the Tertiary Estimand

1. Step 1: At the initial stage, a dataset (named "**MIin3rdEst**") will be constructed, including, per ITT subject (in one dataset record) the following: treatment arm to which subject was randomized to (TRTP), Pooled Country/Geographical Region (CGR1) and Total UPDRS as measured at Baseline (Derived), End of Week 5, End of Week 8 and End of Week 12.

2. Step 2: Using the previously described "**MIin3ndEst**" dataset, the MI procedure using the FCS method with the regression method of classification will be used to generate missing baseline values under the MAR assumption. The number of imputations will be 100 and the procedure will use a seed of 5678 for this imputation step. The SAS® code for this step is provided below:

```
PROC MI DATA=MIin3rdEst OUT=TMP NIMPUTE=100 seed=5678
     minimum=. . 0 maximum=. . 160;
     CLASS trtp CGR1;
     VAR trtp CGR1 bl;
     FCS REG(BL =trtp cgr1);
run;
```

3. Step 3: Thereafter, for each of the 100 imputed datasets, multiple imputations using the method FCS regression missingness will be performed with rasagiline (RAS 0.75) based imputation as control reference under MNAR as its treatment effect is expected to be less prominent among all 4 study arms. The number of imputations will be 1 and the procedure will use a seed of 67891011 with **MINMAXITER=1000** for this imputation step. The SAS® code for this step is provided below:

```
PROC MI data=TMP out=MIout3rdEst NIMPUTE=1 seed=67891011
MINMAXITER=1000
     minimum=. . 0 0 0 0 maximum=. . 160 160 160 160;
     class trtp cgr1;
     VAR cgr1 BL W5 W8 W12;
     FCS regression;
     MNAR model (W5 W8 W12/modelobs=(trtp='RAS 0.75'));
     by _imputation_;
 run;
```

4. Step 4: For each subject within each of the 100 imputed datasets the change from Baseline (Derived) to the End of Week 12 (CHG) will be calculated to be used in the statistical analysis of the change from baseline to Week 12 visit in the total UPDRS score employing the mITT referring to the **Tertiary Estimand**.

16 PRIMARY EFFICACY ENDPOINT AND ANALYSES

The primary efficacy endpoint for this trial will be the change from baseline to Week 12 visit in the total UPDRS score (see for score calculation definition: Unified Parkinson's Disease Rating Scale (UPDRS), defined as sum of UPDRS parts II and III. The mITT analysis set will be used as the principal analysis for efficacy analysis and inference. Main supportive, additional supportive and sensitivity analysis to the main supportive analyses will be conducted with reference to the **Primary Estimand**, **Secondary Estimand** and **Tertiary Estimand**, respectively.

Formal analysis will employ two contrasts: P2B001 vs. PPX and P2B001 vs. RAS.

16.1 PRINCIPAL ANALYSIS OF THE PRIMARY ENDPOINT

The mITT analysis set will be used for the **principal analysis of the primary endpoint**. A Mixed Model for Repeated Measures (MMRM) (SAS® MIXED procedure with REPEATED sub-command) will be used for the analysis of this endpoint. The model will include the following fixed effects: categorical scheduled week by treatment interaction, CGR1, and baseline total UPDRS Score. The model will use the unstructured covariance structure and the REML estimation method and degrees of freedom will be adjusted using the Kenward-Roger method. Data from all three scheduled changes from baseline (derived) to post-baseline visits (weeks 5, 8, and 12) will be used as response in the model and differences between the treatments groups at week 12 will be estimated using contrasts.

The SAS® code planned for the analysis is outlined below:

```
proc mixed Data=ADQS Method=REML;
     ods output LSMeans=LSMmixed Diffs=Diffsmixed;
     Class TRTp visit CGR1;
     Model CHG=TRTp*visit CGR1 BL /DDFM=KR Solution;
     Repeated visit              /Subject=SubjID Type=un;
     LSMeans  TRTp*visit         /Pdiff CL;
where mITT='Yes' and param='Total UPDRS' and Visit in('End of Week
5','End of Week 8','End of Week 12');
run;quit;
```

In case that the model does not converge the strategy outlined in Convergence Issues and Pre-Planned Strategy will be employed.

16.2 MAIN SUPPORTIVE ANALYSIS FOR THE PRIMARY ENDPOINT

This analysis related to the **Primary Estimand** employing the m**ITT Analysis Set** will be considered as the main supportive analysis for the principal analysis of the primary endpoint.

The **MIout1stEst** multiply imputed dataset referring to the **Primary Estimand** will be used in this analysis. The response variable, namely the change from Baseline (Derived) to End of Week 12 visit in the total UPDRS score, of each of the 100 imputed

datasets, will be analyzed using the Analysis of Covariance (ANCOVA) employing the SAS® MIXED procedure. The model will include the planned treatment group (TRTP), CGR1 and baseline total UPDRS score as explanatory variables.

The outcome results of the analyses of the 100 imputed datasets will be combined using the Robin's rules, employing the SAS® MIANALYZE which will be used to derive the combined least squares means (LSM) estimates of the study groups, the between groups contrasts estimates as well as the corresponding 95% CI's and p-values for inference. The SAS® code to be used is outlined below:

```
proc mixed Data=MIout1stEst Method=REML;
     ods output LSMeans=LSmeans1stEst Diffs=Diffs1stEst;
     Class TRTp CGR1;
     Model CHG=TRTp CGR1 BL /Solution;
     LSMeans  TRTp          /Pdiff CL;
    by _imputation_;
run;quit;

* Combining LSmeans *;
*********************;
PROC MIANALYZE DATA=LSmeans1stEst;
     by trtp;
     ODS OUTPUT PARAMETERESTIMATES=LSM1stEstComb;
     MODELEFFECTS estimate;
     STDERR       StdErr;
RUN;

* Combining Between Groups Contrasts *;
**************************************;
PROC MIANALYZE DATA=Diffs1stEst;
     ODS OUTPUT PARAMETERESTIMATES=Contrasts1stEst;
     MODELEFFECTS estimate;
     STDERR       StdErr  ;
      by trtp _trtp;
RUN;
```

16.3 ADDITIONAL SUPPORTIVE ANALYSIS FOR THE PRIMARY ENDPOINT

This analysis related to the **Secondary Estimand** employing the **mITT Analysis Set** will be considered as an additional supportive analysis for the principal analysis of the primary endpoint.

The **MIout2ndEst** multiply imputed dataset referring to the **Secondary Estimand** will be used in this analysis. The analysis of the change from Baseline (Derived) to End of Week 12 visit in the total UPDRS score will be repeated for this multiply imputed dataset as outlined in Section 16.2 with the difference that PROC MIXED will employ the **mITT Analysis Set**, in line with reasons detailed in Randomized Subjects Early Study Terminated During Screening/Baseline Visits and in Missing Observations due to COVID-19.

16.4 SENSITIVITY ANALYSES FOR THE PRINCIPAL ANALYSIS OF THE PRIMARY ENDPOINT

The below sensitivity analyses will be performed to assess the robustness of the results and conclusions derived from the principal analysis of the primary endpoint and its supportive analyses.

16.4.1 Sensitivity Analysis to the Main Supportive Analysis using the Tertiary Estimand

This analysis related to the **Tertiary Estimand** employing the **mITT Analysis Set** will be considered as as a **sensitivity analysis** to the **main supportive analysis**.

The **MIout3rdEst** multiply imputed dataset referring to the **Tertiary Estimand** will be used in this analysis. The analysis of the change from Baseline (Derived) to End of Week 12 visit in the total UPDRS score will be repeated for this multiply imputed dataset as outlined in Section 16.2 with the difference that PROC MIXED will employ the **mITT Analysis Set**, in line with reasons detailed in Randomized Subjects Early Study Terminated During Screening/Baseline Visits and in Missing Observations due to COVID-19.

16.4.2 Additional Sensitivity Analysis to the Main Supportive Analysis using the CO Analysis Set

The **MIout1stEst** multiply imputed dataset referring to the **Primary Estimand** employing the **CO Analysis Set** will be used in this analysis. The analysis of the change from Baseline (Derived) to End of Week 12 visit in the total UPDRS score will be repeated for this multiply imputed dataset as outlined in Section 16.2 with the difference that PROC MIXED will employ the **CO Analysis Set**.

16.4.3 Additional Sensitivity Analysis to the Main Supportive Analysis using the PP Analysis Set

The **MIout1stEst** multiply imputed dataset referring to the **Primary Estimand** employing the **PP Analysis Set** will be used in this analysis. The analysis of the change from Baseline (Derived) to End of Week 12 visit in the total UPDRS score will be repeated for this multiply imputed dataset as outlined in Section 16.2 with the difference that PROC MIXED will employ the **PP Analysis Set**.

16.4.4 Sensitivity Analysis to the Principal Analysis of the Primary Endpoint using the CO Analysis Set

The principal analysis of the primary endpoint described in 16.1 will be repeated for the CO Analysis Set.

16.4.5 Sensitivity Analysis to the Principal Analysis of the Primary Endpoint using the PP Analysis Set

The principal analysis of the primary endpoint described in 16.1 will be repeated for the PP Analysis Set.

16.4.6 Sensitivity Analysis to the Principal Analysis of the Primary Endpoint Accounting for the Potential Unblinding Incident

FDA proposed to *"... repeat the primary efficacy analyses in which all UPDRS Parts 2+3 ratings on affected individuals are treated as missing for all visits taking place after their respective sites received the potentially compromised clinical supplies. For those affected individuals, use the last Parts 2+3 total score prior to the receipt of the unblinded packing lists carried forward to Week 12.*". However, since drug was dispensed at baseline visit, it implies that all post first dose assessments are subjected to the apparent potential unblinding and therefore exclusion of subjects will be performed on a by subject basis.

FDA further proposed to "*... perform the same sensitivity analysis for the secondary efficacy outcome UPDRS Part 2 total score*.".

Accordingly, the following will be performed as part of the sensitivity analysis:

- The principal analysis of the primary endpoint described in 16.1 will be repeated for the mITT Analysis Set excluding subjects with potential unblinding incident.
- The primary analysis for the secondary endpoint, the change from baseline (derived) to end of week 12 in motor UPDRS (part III) score described in Section 17.2 will be repeated for the mITT Analysis Set excluding subjects with potential unblinding incident.
- The primary analysis for the secondary endpoint, the change from baseline to end of week 12 in ADL UPDRS score described in Section 17.3 will be repeated for the mITT Analysis Set excluding subjects with potential unblinding incident.

16.4.7 Tipping Point Analysis

The Tipping Point Analysis will use the **Primary Estimand** multiply imputed **MIout1stEst** dataset described in Section 15.4.1 with the aim of exploring the possible impact of missing values on the results and conclusions derived from the main supportive analysis of the primary endpoint performed with reference to the mITT Analysis Set for the Primary Estimand. This analysis will be performed according to the following steps:

1. Missing changes from baseline to week 12 calculated following multiple imputation of missing values for subjects of the P2B001 arm will artificially be increased (negative change from baseline reflects improvement) by the value of δ ($\delta \geq 0$).
2. The main supportive analysis for the primary endpoint as described in Section 16.2 will be employed for the two contrasts: P2B001 vs. RAS and P2B001 vs. PPX.

The maximal p-value derived from the two contrasts as well as the minimal p-value will be accumulated for each value of δ.

3. Steps 1 and 2 will be repeated by steps of 0.1 increasing increments of δ. Note that δ=0 corresponds to results obtained according to Section 16.2 avoiding artificially increasing the missing values multiply imputed values of the P2B001 subjects. The first δ in which significance is lost for the maximal p-value (endpoint is met only if both contrasts are met) will then be considered as the tipping point.
4. The maximal p-values and the minimal p-values obtained for the grid of δ will graphically be displayed to visualize this sensitivity analysis.

16.4.8 Descriptive Subgroups Analysis

This study was not powered for subgroup analyses and therefore all of the analyses proposed below will be conducted in an exploratory manner.

The descriptive statistics of changes from baseline in the total UPDRS for the mITT Analysis Set will be displayed for the following subgroups:

- Gender.
- Study population (North Americans or Non North Americans)
- Age (<=Median ITT Age, > Median ITT Age)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Other)

17 SECONDARY EFFICACY ENDPOINT AND ANALYSES

The **mITT** analysis set will be used as the primary analysis set for efficacy analysis and inference for the secondary endpoints defined below. Supportive analyses for these secondary endpoints will be conducted using the **Primary Estimand**. Endpoints and analyses are governed by the order of contrasts testing according to Significance Level and Multiplicity Adjustment.

17.1 1ST SECONDARY EFFICACY ENDPOINT: CHANGE FROM BASELINE TO END OF WEEK 12 IN TOTAL ESS SCORE

The ESS analyses will use definitions outlined in Epworth Sleepiness Scale (ESS).

Formal analysis will test the P2B001 vs. PramiER contrast in the change from Baseline (Derived) to End of Week 12 in Epworth Sleepiness Scale (ESS).

The primary statistical analysis for this secondary endpoint will use the mITT Analysis Set employing the MMRM model as described in the Principal Analysis of the Primary Endpoint. BL, W5, W8 and W12 values are those referred to the Total ESS Score.

Supportive analysis for this secondary endpoint will use:

- Multiple Imputations step as described in Multiple Imputations for the Primary Estimand with one difference: maximal imputed values at BL, W5, W8 and W12 will be bounded by the maximal value of **24**.
- Statistical analysis of 100 multiply imputed datasets for the **Primary Estimand** will use an ANCOVA as described in the Main Supportive Analysis for the Primary Endpoint and will be followed by two MIANALYZE steps to combine the least square means and the between groups contrasts.

17.2 2ND SECONDARY EFFICACY ENDPOINT: CHANGE FROM BASELINE (DERIVED) TO END OF WEEK 12 IN MOTOR UPDRS (PART III) SCORE

The Motor UPDRS analyses will use definitions outlined in Unified Parkinson's Disease Rating Scale (UPDRS).

The primary statistical analysis for this secondary endpoint will use the MMRM model as described in the Principal Analysis of the Primary Endpoint. BL, W5, W8 and W12 values are those referred to the Motor UPDRS Score.

Supportive analysis for this exploratory endpoint will use:

- Multiple Imputations step as described in Multiple Imputations for the Primary Estimand with one difference: maximal imputed values at BL, W5, W8 and W12 will be bounded by the maximal value of **108**.

- Statistical analysis of the 100 multiply imputed datasets for the **Primary Estimand** will use an ANCOVA as described in the Main Supportive Analysis for the Primary Endpoint and will be followed by two MIANALYZE steps to combine the least square means and the between groups contrasts.

17.3 3RD SECONDARY EFFICACY ENDPOINT: CHANGE FROM BASELINE TO END OF WEEK 12 IN ADL UPDRS SCORE

The ADL UPDRS analyses will use definitions outlined in Unified Parkinson's Disease Rating Scale (UPDRS).

Formal analysis will test the change from Baseline (Derived) to End of Week 12 visit in ADL UPDRS Score employing two contrasts: P2B001 vs. PPX and P2B001 vs. RAS.

The primary statistical analysis for this secondary endpoint will use the mITT Analysis Set employing the MMRM model as described in the Principal Analysis of the Primary Endpoint. BL, W5, W8 and W12 values are those referred to the ADL UPDRS Score.

Supportive analysis for this secondary endpoint will use:

- Multiple Imputations step as described in Multiple Imputations for the Primary Estimand with one difference: maximal imputed values at BL, W5, W8 and W12 will be bounded by the maximal value of **52**.
- Statistical analysis of 100 multiply imputed datasets for the **Primary Estimand** will use an ANCOVA as described in the Main Supportive Analysis for the Primary Endpoint and will be followed by two MIANALYZE steps to combine the least square means and the between groups contrasts.

17.4 4TH SECONDARY EFFICACY ENDPOINT: CHANGE FROM BASELINE TO END OF WEEK 12 IN ADL SUBSCALE SCORE OF PDQ39

The ADL subscale of the PDQ39 analyses will use definitions outlined in Parkinson's Disease Quality of Life Questionnaire (PDQ39).

Formal analysis will test the change from Baseline (Derived) to End of Week 12 visit in ADL subscale score of PDQ39 employing three contrasts according to the testing order specified in Significance Level and Multiplicity Adjustment: Firstly, P2B001 vs. PramiER and thereafter, if met, P2B001 vs. PPX and P2B001 vs. RAS. BL and W12 values are those referred to the ADL subscale of PDQ39.

The primary statistical analysis for this secondary endpoint will use the mITT Analysis Set using the Analysis of Covariance (ANCOVA) employing the SAS® MIXED procedure. The model will include the planned treatment group (TRTP), CGR1 and baseline score as explanatory variables. The least squares means (LSM) estimates of the study groups, the between groups contrasts estimates as well as the corresponding

95% CI's and p-values for inference will be displayed. The SAS® code to be used is outlined below:

```
proc mixed Data=&dataset Method=REML;
     ods output LSMeans=LSmeans Diffs=Diffs;
     Class TRTp CGR1;
     Model CHG=TRTp CGR1 BL /Solution;
     LSMeans  TRTp          /Pdiff CL;
run;quit;
```

Supportive analysis for this secondary endpoint will use:

- Multiple Imputations step as described in Multiple Imputations for the Primary Estimand with the following differences:
  - ✓ As PDQ39 was collected at Baseline Visit and at the End of Week 12 the SAS® code referring to W5 and W8 will be omitted.
  - ✓ Maximal imputed values at BL and W12 will be bounded by the maximal value of **100**.
- Statistical analysis of 100 multiply imputed datasets for the **Primary Estimand** will use an ANCOVA as described in the Main Supportive Analysis for the Primary Endpoint and will be followed by two MIANALYZE steps to combine the least square means and the between groups contrasts.

17.5 5TH SECONDARY EFFICACY ENDPOINT: CHANGE FROM BASELINE TO END OF WEEK 12 IN TOTAL PDQ39 SCORE

The ADL subscale of the PDQ39 analyses will use definitions outlined in Parkinson's Disease Quality of Life Questionnaire (PDQ39).

Formal analysis will test the change from Baseline (Derived) to End of Week 12 visit in total PDQ39 score employing two contrasts according to the testing order specified in Significance Level and Multiplicity Adjustment: P2B001 vs. PPX and P2B001 vs. RAS. BL and W12 values are those referred to the total PDQ39 score.

Primary statistical analysis for this secondary endpoint as well as supportive analysis for this secondary endpoint will be conducted as described in Section 17.4.

18 EXPLORATORY ENDPOINTS AND ANALYSES (P2B001 VS. COMPONENTS)

Analyses of the exploratory endpoints will provide additional insight into the therapeutic effect of **P2B001 as compared to its two components**. The **mITT** Analysis Set will be used as the primary analysis set for effectiveness analysis for the below exploratory endpoints. Supportive assessments for these exploratory endpoints will be conducted using the **Primary Estimand** employing the mITT. Results will be provided displaying the model derived estimates and 95% CIs, the magnitude of treatment effect and 95% CIs, as well as nominal p-values.

The exploratory endpoints to be analyzed are:

18.1 END OF WEEK 12 CGI-S RESPONDERS ANALYSIS

The End of Week 12 Responders analyses for CGI-S will use definitions outlined in Clinical Global Impression – Severity Scale (CGI-S).

18.1.1 Primary CGI-S Responders Analysis

The primary statistical analysis for this exploratory endpoint will use logistic regression (SAS® PROC LOGISTIC) and model will include the following fixed effects: TRTp, CGR1, and baseline CGI-S Score (as 1 df variable). The response classification ("Responder"/"Non-Responder") will be used as response in the model.

The SAS® code to be used is outlined below:

```
proc logistic data=&dataset order=internal descending;
     ODS output CLOddsWald=CLOddsWald Diffs=Diffs LSmeans=LSMeans;
     class cgr1;
     class TRTp (ref='P2B001') / param=ref param=glm;
     model Response = TRTp CGR1 BL  / cl risklimits expb;
     lsmeans TRTp / cl ilink pdiff;
run;quit;
```

18.1.2 Supportive CGI-S Responders Analysis

Supportive analysis for this exploratory endpoint will be conducted with reference to the **Primary Estimand** as described below:

18.1.2.1 Multiple Imputations (CGI-S Responders Analysis)

1. Step 1: At the initial stage, a dataset (named "**MIin1stEst**") will be constructed, including, per mITT subject (in one dataset record) the following: treatment arm to which subject was randomized to (TRTP), Pooled Country/Geographical Region (CGR1) and CGI-S at Baseline (Derived) and at End of Week 12. Observations of **MIin1stEst** collected post rescue therapy initiation, as well as post last P2B/Placebo administration date of ETT for whatever reason will be set to missing values.

2. Step 2: The MI procedure, using the FCS method (SAS® MI procedure with the logistic method of classification variables) will be used for MI under the missing at random (MAR) assumption. The number of imputations will be 100 and procedure will use a seed of 1357. The SAS® code for this step is provided below:

```
proc MI Data=MIin1stEst Out=TMP Nimpute=100 Seed=1357;
     Class TRTp CGR1 W12;
     Var TRTp CGR1 BL W12;
     FCS logistic(W12 = TRTp CGR1 BL);
run;quit;
```

3. Step 3: Scores multiply imputed in previous step under MAR following rescue therapy will then be set to missing values in all 100 imputed datasets for the purpose of MI under MNAR. Thereafter, for each of the 100 imputed datasets, multiple imputations using the method for monotone regression missingness will be performed with rasagiline (RAS 0.75) based imputation as control reference under MNAR. The number of imputations will be 1 and the procedure will use a seed of 3579 for this imputation step. The SAS® code for this step is provided below:

```
PROC MI data=TMP1 out=MIout1stEst NIMPUTE=1 seed=3579
     minimum=. . 0 0 maximum=. . 7 7;
     class trtp cgr1;
     VAR cgr1 BL W12;
     monotone regression;
     MNAR model (W12/modelobs=(trtp='RAS 0.75'));
     by _imputation_;
run;
```

4. Step 4: For each subject within each of the 100 imputed datasets the change from Baseline (Derived) to the End of Week 12 (CHG), following the rounding to nearest integer of imputed values, will be calculated and the subject will be classified as a "Responder" or a "Non-Responder" as outlined in Clinical Global Impression – Severity Scale (CGI-S).

18.1.2.2 Statistical Analysis of the Multiply Imputed Datasets (CGI-S Responders Analysis)

The statistical analysis of the multiply imputed datasets will be conducted as outlined below:

1. Step 1: Each of the 100 imputed datasets will be analyzed for the between groups contrasts in this response variable. Analyses will use logistic regression (SAS® PROC LOGISTIC) and model will include the following fixed effects: TRTp, CGR1, and baseline CGI-S Score (as 1 df variable). The response classification ("Responder"/"Non-Responder") will be used as response in the model.

   The SAS® code to be used at this stage is:

```
proc logistic data=MIout1stEst order=internal descending;
     ODS output CLOddsWald=CLOddsWaldMI
                ParameterEstimates=ParameterEstimatesMI
                LSmeans=LSMeansMI;
     class cgr1;
     class TRTp (ref='P2B001') / param=ref param=glm;
     model Response = TRTp CGR1 BL  / cl risklimits expb;
     lsmeans TRTp / cl ilink;
     by _imputation_;
run;quit;
```

2. Step 2: Then, the 100 WALD test statistics will directly be combined applying the Wilson-Hilferty transformation to normalize the test statistic and results will be combined using Rubin's rule to obtain the p-value using the below SAS® code:

```
* Wilson-Hilferty Transformation to the WALD Statistics *;
data WALD;set ParameterEstimatesMI;
     WALD_value_WilHil=((WaldChiSq/DF)**(1/3) -
                        (1-2/(9*DF)))/SQRT(2/(9*DF));
     WALD_sterr_WilHil=1.0;
     if classval0 in('PramiER','PPX 0.6','RAS 0.75');
     contrast=trim(classval0)||' vs P2B001';
     keep contrast WaldChiSq DF WALD_sterr_WilHil
                                WALD_value_WilHil;
 run;

 * Combine Results *;
 PROC MIANALYZE data=WALD;
      by contrast;
      ODS output ParameterEstimates=MI_p_value;
      modeleffects WALD_value_WilHil;
      stderr       WALD_sterr_WilHil;
 run;

* Compute p-value from the Combined CMH Test *;
data MI_p_value;set MI_p_value;
     if tValue>0 then Prob_upper=Probt/2;
      else Prob_upper=1-probt/2;
      keep contrast Prob_upper;
run;
```

3. Step 3: The magnitude of treatment effect will use the Odds Ratio. As the odds-ratio is not expected to be normally distributed, analysis will be conducted on the log transformed odds-ratio. Standard error will be derived from the log transformed confidence interval of the odds-ratio. Back transformed estimate and its 95% confidence interval will be used to derive the combined estimate (Rubin's Rules). The SAS® code to be used for these procedures is provided below:

```
* Log-transform odds ratio estimates and obtain SE from CI *;
data CLOddsWaldMI;SET CLOddsWaldMI;
     log_or_value=LOG(OddsRatioEst);
     log_or_se=(LOG(UpperCL)-LOG(LowerCL))/(2*1.96);
     if effect in('TRTP PramiER  vs P2B001',
                  'TRTP PPX 0.6  vs P2B001',
                  'TRTP RAS 0.75 vs P2B001');
       contrast=left(tranwrd(Effect,'TRTP ',''));
       keep contrast log_or_value log_or_se;
run;
proc sort data=CLOddsWald;by contrast;run;

* Combine the Log-transformed Odds-Ratio *;
PROC MIANALYZE DATA=CLOddsWaldMI;
     by contrast;
     ODS OUTPUT PARAMETERESTIMATES=PARAMETERESTIMATES_OR;
     MODELEFFECTS log_or_value;
     STDERR       log_or_se;
run;

* Back-transform combined values *;
DATA PARAMETERESTIMATES_OR;SET PARAMETERESTIMATES_OR;
     Estimate_back = EXP(ESTIMATE);
     LCL_back=Estimate_back*EXP(-1.96*STDERR);
     UCL_back=Estimate_back*EXP(+1.96*STDERR);
      keep contrast Estimate_back LCL_back UCL_back;
run;
```

4. Step 4: The model adjusted combined (Rubin's Rules) estimated proportion of responders will then be obtained using the below SAS® code:

```
* Combined LSMeans for model adjusted responders proportions *;
proc sort data=LSMeansMI;by TRTp;run;
PROC MIANALYZE DATA=LSMeansMI;
     by TRTp;
     ODS OUTPUT PARAMETERESTIMATES=PARAMETERESTIMATES_LSmeans;
     MODELEFFECTS Mu;
     STDERR       StderrMu;
run;
```

18.2 END OF WEEK 12 TOTAL UPDRS RESPONDERS ANALYSIS

The End of Week 12 Responders analyses for Total UPDRS responder's analysis will use definitions outlined in Unified Parkinson's Disease Rating Scale (UPDRS).

The primary statistical analysis for this exploratory endpoint will be conducted as described in Section 18.1.1 with the difference of using the Total UPDRS Response variable ("Responder"/"Non-Responder") adjusted to baseline Total UPDTS score.

Supportive analysis for this exploratory endpoint will be conducted with reference to the **Primary Estimand** as described below:

- Multiple Imputations will be conducted as outlined in Section 15.4.1 with the following addition to Step 4: The change from Baseline (Derived) to the End of Week 12 (CHG) will be used to define the Total UPDRS binary response variable: A subject with an improvement of 4 points or more will be classified as a "Responder". Otherwise, the subject will be defined as a "Non-Responder".
- Statistical analyses of the multiply imputed data sets will be conducted as outlined in Section 18.1.2.2 with the difference of using the Total UPDRS binary response variable ("Responder"/"Non-Responder") and the Total UPDRS baseline value.

18.3 CHANGE FROM BASELINE TO END OF WEEK 12 IN TOTAL ESS SCORE

The analysis of the change from Baseline to End of Week 12 in the Total ESS score is detailed in 1st Secondary Efficacy Endpoint: Change from Baseline to End of Week 12 in Total ESS Score. The analyses of the P2B001 vs. its components will accordingly be conducted as an exploratory endpoint analysis.

18.4 CHANGE FROM BASELINE (DERIVED) TO END OF WEEK 12 IN THE PDQ39 SUBSCALES SCORES

The analyses of the PDQ39 subscales will use definitions outlined in Parkinson's Disease Quality of Life Questionnaire (PDQ39).

Please note that the analysis plan for the change from baseline (derived) to End of Week 12 in the PDQ39 ADL subscale and in the Total PDQ39 score were already outlined as part of the analyses of the secondary endpoints and therefore are not repeated in this section. Within this work frame of exploratory endpoints analyses, the following subscales will be analyzed, each separately:

- Mobility Score
- Emotional Well-Being Score
- Stigma Score
- Social Support Score
- Cognitive Impairment Score
- Communications Score
- Bodily Discomfort Score

Analysis of each of the above subscales will be performed as outlined in 4th Secondary Efficacy Endpoint: Change from Baseline to End of Week 12 in ADL Subscale Score of PDQ39.

18.5 CHANGE FROM BASELINE (DERIVED) IN THE IMPULSIVE-COMPULSIVE DISORDERS IN PD (QUIP-RS) TOTAL SCORE AND SUBSCALES SCORES

The QUIP-RS analyses will use definitions outlined in Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-Rating Scale).

Within this scope of work, a total of 8 aggregate metrics will be analyzed, each separately for the Change from Baseline (Derived) to End of Week 12:

- Total QUIP-RS Score
- Total ICD Score
- Total Gambling Score
- Total Sex Score
- Total Buying Score
- Total Eating Score
- Total Hobbyism-Punding Score
- Total Medications Score

The statistical analysis for each of these 8 aggregated exploratory endpoints will use the MMRM model as described in the Principal Analysis of the Primary Endpoint. BL, W3, W5, W12 and W14 values are those referred to the each of the aggregate metrics above listed.

18.6 CHANGE FROM BASELINE (DERIVED) TO END OF WEEK 12 IN THE SUMMARY SCORES OF HEALTH-RELATED QUALITY OF LIFE (HRQOL) SF-12V2

The HRQOL SF-12v2 analyses of the two summary scores will use definitions outlined in Health-Related Quality of Life (HRQOL) SF-12v2.

Within this scope of work, two norm based scores will be analyzed, each separately:

- Mental Component Summary Score.
- Physical Component Summary Score.

The primary statistical analysis for each of these exploratory endpoints will use the mITT Analysis Set using the Analysis of Covariance (ANCOVA) employing the SAS® MIXED procedure. The model will include the planned treatment group (TRTP), CGR1 and baseline score as explanatory variables. The least squares means (LSM) estimates of the study groups, the between groups contrasts estimates as well as the corresponding 95% CI's and nominal p-values will be displayed. The SAS® code to be used is outlined below:

```
proc mixed Data=&dataset Method=REML;
     ods output LSMeans=LSmeans Diffs=Diffs;
     Class TRTp CGR1;
     Model CHG=TRTp CGR1 BL /Solution;
     LSMeans  TRTp          /Pdiff CL;
run;quit;
```

Supportive analysis for each of these exploratory endpoints will use:

- Multiple Imputations step as described in Multiple Imputations for the Primary Estimand with the following differences:
  - ✓ As SF-12V2 was collected at Baseline Visit and at the End of Week 12 the SAS® code referring to W5 and W8 will be omitted.
  - ✓ Maximal imputed values at BL and W12 will be bounded by the maximal value of **100**.
- Statistical analysis of 100 multiply imputed datasets for the **Primary Estimand** will use an ANCOVA as described in the Main Supportive Analysis for the Primary Endpoint and will be followed by two MIANALYZE steps to combine the least square means and the between groups contrasts.

18.7 END OF WEEK 12 CGI-I RESPONDERS ANALYSIS

The End of Week 12 Responders analyses for CGI-I responders analysis will use definitions outlined in Clinical Global Impression – Improvement Scale (CGI-I).

The primary statistical analysis for this exploratory endpoint will use the GLIMMIX procedure for binary outcome measure with logit link function. The model will include the interaction between the treatment group and visit and CGR1 as fixed factors and the response classification ("Responder"/"Non-Responder") will be used as response in the model. Note that Analysis will model the probability of "Responder". The SAS® code to be used is outlined below:

```
proc glimmix data=ADQS;
     ODS output Diffs=Diffs LSmeans=LSMeans;
     class SubjID TRTp VISIT cgr1;
     model Response(event='Responder') = TRTp*Visit CGR1 /
           LINK=LOGIT DIST=binary DDFM=KR;
     RANDOM INT / sub=SubjID;
     lsmeans Visit*TRTp / cl ilink pdiff oddsratio;
     where mITT='Yes' and QSCAT='CGI' and Param='CGI-Improvement'
     and Visit in('End of Week 5','End of Week 8','End of Week 12');
run;quit;
```

Supportive analysis for this exploratory endpoint will be conducted with reference to the **Primary Estimand** as described below:

- Multiple Imputations will be conducted as outlined below:

1. Step 1: At the initial stage, a dataset (named "**MIin1stEst**") will be constructed, including, per mITT subject (in one dataset record) the following: treatment arm to which subject was randomized to (TRTP), Pooled Country/Geographical Region (CGR1) and CGI-I at End of Week 5, End of Week 8 and at End of Week 12. Observations of **MIin1stEst** collected post rescue therapy initiation, as well as post last P2B/Placebo administration date of ETT for whatever reason will be set to missing values.

2. Step 2: The MI procedure, using the FCS method (SAS® MI procedure with the logistic method of classification variables) will be used for MI under the missing at random (MAR) assumption. The number of imputations will be 100 and procedure will use a seed of 3579. The SAS® code for this step is provided below:

```
* Multiple Imputations for the Primary Estimand *;
proc MI Data=MIin1stEst Out=TMP Nimpute=100 Seed=3579;
     Class TRTp CGR1 W12;
     Var TRTp CGR1 W5 W8 W12;
     FCS logistic(W12 =TRTp CGR1);
run;quit;
```

3. Step 3: Scores multiply imputed in previous step under MAR following rescue therapy will then be set to missing values in all 100 imputed datasets for the purpose of MI under MNAR. Thereafter, for each of the 100 imputed datasets, multiple imputations using the method for monotone regression missingness will be performed with rasagiline (RAS 0.75) based imputation as control reference under MNAR. The number of imputations will be 1 and the procedure will use a seed of 57911 for this imputation step. The SAS® code for this step is provided below:

```
PROC MI data=TMP1 out=MIout1stEst NIMPUTE=1 seed=57911
     minimum=. . 0 0 0 maximum=. . 7 7 7;
     class trtp cgr1;
     VAR cgr1 W5 W8 W12;
     monotone regression;
     MNAR model (W5 W8 W12/modelobs=(trtp='RAS 0.75'));
     by _imputation_;
run;
```

4. Step 3: For each subject within each of the 100 imputed datasets, following the rounding to nearest integer of imputed values, a subject will be classified as a "Responder" or a "Non-Responder" as outlined in Clinical Global Impression – Improvement Scale (CGI-I).

- Statistical analyses of the CGI-I multiply imputed data sets will be conducted as outlined in Section 18.1.2.2 with the difference of using the Total CGI-I binary response variable at 'End of Week 12' while omitting BL value in the PROC LOGISTIC model statement.

19 ADDITIONAL EXPLORATORY ENDPOINTS AND ANALYSES (P2B001 VS. PRAMI-ER)

Analyses of the additional exploratory endpoints will provide further insight into the therapeutic effect of **P2B001 as compared PramiER**. The **mITT** Analysis Set will be used as the primary analysis set for effectiveness analysis for the below additional exploratory endpoints and supportive assessments for these will be conducted using the **Primary Estimand**. Results will be provided displaying the model derived estimates and 95% CIs, the magnitude of treatment effect and 95% CIs, as well as nominal p-values.

The additional exploratory endpoints to be analyzed are:

19.1 CHANGE FROM BASELINE (DERIVED) TO END OF WEEK 12 IN TOTAL UPDRS (PART II AND III) SCORE

The Total UPDRS analyses will use definitions outlined in Unified Parkinson's Disease Rating Scale (UPDRS).

The primary statistical analysis for this exploratory endpoint will use the MMRM model as described in the Principal Analysis of the Primary Endpoint. BL, W5, W8 and W12 values are those referred to the Total UPDRS Score.

Supportive analysis for this exploratory endpoint will use:

- Multiple Imputations step as described in Multiple Imputations for the Primary Estimand.
- Statistical analysis of the 100 multiply imputed datasets for the **Primary Estimand** will use an ANCOVA as described in the Main Supportive Analysis for the Primary Endpoint and will be followed by two MIANALYZE steps to combine the least square means and the between groups contrasts.

19.2 CHANGE FROM BASELINE (DERIVED) TO END OF WEEK 12 IN MOTOR UPDRS (PART III) SCORE

The Motor UPDRS analyses will use definitions outlined in Unified Parkinson's Disease Rating Scale (UPDRS).

The primary statistical analysis for this exploratory endpoint will use the MMRM model as described in the Principal Analysis of the Primary Endpoint. BL, W5, W8 and W12 values are those referred to the Motor UPDRS Score.

Supportive analysis for this exploratory endpoint will use:

- Multiple Imputations step as described in Multiple Imputations for the Primary Estimand with one difference: maximal imputed values at BL, W5, W8 and W12 will be bounded by the maximal value of **108**.

- Statistical analysis of the 100 multiply imputed datasets for the **Primary Estimand** will use an ANCOVA as described in the Main Supportive Analysis for the Primary Endpoint and will be followed by two MIANALYZE steps to combine the least square means and the between groups contrasts.

19.3 CHANGE FROM BASELINE TO END OF WEEK 12 IN ADL UPDRS SCORE

The ADL UPDRS analyses will use definitions outlined in Unified Parkinson's Disease Rating Scale (UPDRS).

The primary statistical analysis for this exploratory endpoint will use the MMRM model as described in the Principal Analysis of the Primary Endpoint. BL, W5, W8 and W12 values are those referred to the Motor UPDRS Score.

Supportive analysis for this exploratory endpoint will use:

- Multiple Imputations step as described in Multiple Imputations for the Primary Estimand with one difference: maximal imputed values at BL, W5, W8 and W12 will be bounded by the maximal value of **52**.
- Statistical analysis of the 100 multiply imputed datasets for the **Primary Estimand** will use an ANCOVA as described in the Main Supportive Analysis for the Primary Endpoint and will be followed by two MIANALYZE steps to combine the least square means and the between groups contrasts.

19.4 END OF WEEK 12 CGI-S RESPONDERS ANALYSIS

The End of Week 12 Responders analysis for CGI-S for the P2B001 vs. Prami ER contrast will use the methodology outlined in Section 18.1 using the mITT Analysis Set.

19.5 END OF WEEK 12 TOTAL UPDRS RESPONDERS ANALYSIS

The End of Week 12 total UPDRS responders analysis for the P2B001 vs. Prami ER contrast will use the methodology outlines in Section 18.2 using the mITT Analysis Set.

19.6 END OF WEEK 12 CGI-I RESPONDERS ANALYSIS

The End of Week 12 Responders analysis for CGI-I for the P2B001 vs. Prami ER contrast will use the methodology outlines in Section 18.7 using the mITT Analysis Set.

19.7 CHANGE FROM BASELINE (DERIVED) TO END OF WEEK 12 IN THE PDQ39 SUBSCALES SCORES

The analyses of the change from baseline (Derived) to the end of Week 12, evaluating the P2B001 vs. PramiER contrast will be conducted for all of the PDQ39 aggregate scores excluding the PDQ39 ADL subscale which was already outlined as part of the analyses of the secondary endpoints and therefore is not repeated in this section.

Analysis of each of these aggregates will be performed as outlined in 5th Secondary Efficacy Endpoint: Change from Baseline to End of Week 12 in Total PDQ39 Score.

19.8 PROPORTION (%) OF PATIENTS WITH POST-BASELINE ESS SCORE >10

The analysis of this binary outcome measure will use definitions outlined in Epworth Sleepiness Scale (ESS). Analysis will be conducted using the mITT Analysis Set.

The primary statistical analysis for this exploratory endpoint will use logistic regression (SAS® PROC LOGISTIC) and model will include the following fixed effects: TRTp, CGR1, and baseline Total ESS Score (as 1 df variable). The response classification ("Post-Baseline ESS>10"/"Otherwise") at any time post baseline will be used as response in the model. Note that Analysis will model the probability of ("Post-Baseline ESS>10". The SAS® code to be used is outlined below:

```
proc logistic data=&dataset order=internal descending;
        ODS output CLOddsWald=CLOddsWald
            ParameterEstimates=ParameterEstimates LSmeans=LSMeans;
        class cgr1;
        class TRTp (ref='P2B001') / param=ref param=glm;
        model Response = TRTp CGR1 BL  / cl risklimits expb;
        lsmeans TRTp / cl ilink;
run;quit;
```

Supportive analysis for this exploratory endpoint will be conducted with reference to the **Primary Estimand** as described below:

- Multiple Imputations will be conducted as outlined in Section 15.4.1 but Step 4 will read as follows:

  Step 4: For each subject within each of the 100 imputed datasets, any post baseline observation of Total ESS >10 will identify a subject as "Post-Baseline ESS>10". Otherwise, a subject will be classified as " Otherwise".

- Statistical analyses of the multiply imputed data sets will be conducted as outlined in Section 18.1.2.2 with the difference of using this binary response variable and the Total ESS baseline value.

19.9 PROPORTION (%) OF PATIENTS WITH ESS SCORE ≤10 AT BASELINE AND ESS SCORE >10 POST-BASELINE

The analysis of this binary outcome measure will use definitions outlined in Epworth Sleepiness Scale (ESS). Analysis will be conducted using the mITT Analysis Set.

The primary statistical analysis for this exploratory endpoint will use logistic regression (SAS® PROC LOGISTIC) and model will include the following fixed effects: TRTp, CGR1, and baseline Total ESS Score (as 1 df variable). The response classification ("ESS≤10→ESS>10"/" Otherwise "), namely the shift from baseline to any time post-baseline, will be used as response in the model. Note that Analysis will model the probability of "ESS≤10→ESS>10". The SAS® code to be used is outlined below:

```
proc logistic data=&dataset order=internal descending;
        ODS output CLOddsWald=CLOddsWald
            ParameterEstimates=ParameterEstimates LSmeans=LSMeans;
        class cgr1;
        class TRTp (ref='P2B001') / param=ref param=glm;
        model Response (event='ESS<=10 -> ESS>10') = TRTp CGR1 BL  /
              cl risklimits expb;
        lsmeans TRTp / cl ilink;
run;quit;
```

Supportive analysis for this exploratory endpoint will be conducted with reference to the **Primary Estimand** as described below:

- Multiple Imputations will be conducted as outlined in Section 15.4.1 but Step 4 will read as follows:

  Step 4: For each subject within each of the 100 imputed datasets, any post baseline of observation >10 with baseline measurement ≤10 will identify a subject as "ESS≤10→ESS>10". Otherwise, a subject will be classified as " Otherwise".

- Statistical analyses of the multiply imputed data sets will be conducted as outlined in Section 18.1.2.2 with the difference of using this binary response variable and the Total ESS baseline value.

20 SAFETY ANALYSES

All safety analyses specified herein pertain to the ST Analysis Set using the **ST Analysis Set denominator** unless otherwise specified.

20.1 ANALYSES OF ADVERSE EVENTS

20.1.1 Treatment Emergent AEs

Adverse events were recorded from the time when a subject has signed the Informed Consent Form till the then end of the safety follow-up visit. The MedDRA dictionary was used to standardize the terms used by the investigator to describe the Adverse Events (AEs).

The following will be incorporated into the analysis of adverse events:

- All analyses to be provided will include only coded AEs.
- Adverse events analyses will include only the Treatment Emergent Adverse Events (TEAEs), namely, those events which started on the day of first study IP administration or afterwards. Both TEAEs and non-TEAES will be listed.

The following AEs analyses will be provided:

- The incidence (no. of patients) and frequency (no. of events) of TEAEs will be provided when broken down by System Organ Class (SOC), and by SOC and Preferred Term (PT) according to MedDRA dictionary. Note that PT is referred to the database Dictionary derived term.
- Breakdowns of TEAEs by all of the AEs attributes will also be provided.
- The derived dictionary used in the analyses displaying the MedDRA System Organ Class (SOC), the Preferred Term (PT) and the AE Verbatim Term as specified by the Investigator, will be provided.
- SAEs, if any, as captured in the clinical database will be listed.
- Summary tables of TEAEs including TEAEs reported for those subjects that EST or ETT will also be provided.
- Summary tables of TEAEs including TEAEs reported for those subjects that EST or ETT due to adverse events will also be provided.

20.1.2 TEAEs of Special Interest

The incidence and frequency of TEAE of special interest will also be summarized using descriptive statistics. These include:

- **Sleep Related** (e.g., PT terms: Disturbances in sleep phase rhythm, Poor quality sleep, Disturbances in initiating and maintaining sleep (Insomnia), Parasomnias, Sleep disorder, Narcolepsy and associated conditions)

- **Dopaminergic AEs** (e.g., PT terms: somnolence, nausea, vomiting, Orthostatic hypotension, Hallucinations, hallucinations gustatory, hallucination visual, hallucinations auditory, Gambling disorder, Compulsive shopping, Obsessive thoughts, Obsessive-compulsive, Impulsive behaviour, impulsive–control disorder)
- **Depression/Mood**: (e.g., PT terms: Depression, Anxiety symptoms, Depressed mood, Major depression, Restlessness, Apathy)
- **ICD/OCD**: (e.g., PT terms: Gambling disorder, Compulsive shopping, Obsessive thoughts, Obsessive-compulsive, Impulsive behavior, impulsive– control disorder)
- **GI Disorders**: (e.g., PT terms: Nausea, Vomiting, Diarrhoea, Constipation, Abdominal pain upper, Abdominal discomfort, Gastritis, Dyspepsia, Gastroesophageal reflux disease, Flatulence)
- **OH Related**: (e.g., PT terms: Dizziness, Orthostatic hypotension, Dizziness postural, Dizziness exertional, Fall, Hypotension, Syncope)
- **Daytime Sleepiness Related**: (e.g., Sudden onset of sleep, Somnolence)

Temporal pattern of AEs of special interest will also be displayed when broken down by the time to events onset as described in 20.1.3 and in 20.1.4.

20.1.3 Time to Event Onset (Temporal Pattern of AEs)

Time to events onset analyses will use the following categories:

- <=7 Days, >7 Days

For these time categories, the incidence and frequency of TEAE by time category in which TEAEs were reported will be displayed using descriptive statistics.

20.1.4 Further Temporal Pattern of AEs

TEAEs of special interest (see TEAEs of Special Interest) will be displayed using graphical presentations as proposed by Olanow et al [Movement Disorders, 2018, wileyonlinelibrary.com DOI: 10.1002/mds.27497]

20.2 Analyses of Laboratory Data

Safety laboratory tests (chemistry, hematology, coagulation and urinalysis), conducted at screening, safety follow up visit, and additional liver function or kidney function tests, as needed, will be carried out by the Eurofins Central Laboratory EU for sites in Europe and Eurofins Central Laboratory US for sites in USA and Canada.

Any clinically important abnormal laboratory values noted at the Screening visit will be recorded as medical history. In addition, in order for the Sponsor to collect additional information about clinically important laboratory abnormalities, at

minimum, the following laboratory abnormalities should be captured from Baseline and onwards on the AE pages of the eCRF as appropriate:

- Any laboratory test result that meets the criteria for an AE or SAE;
- Any laboratory abnormality that requires the subject to have study drug discontinued or interrupted;
- Any laboratory abnormality that requires the subject to receive specific corrective therapy.

All clinically important abnormal laboratory tests occurring during the study will be repeated in appropriate intervals until: (1) the value returns to Baseline, (2) the value is judged to be clinically acceptable by the Investigator and the Sponsor, (3) a diagnosis that explains the abnormal laboratory is made or (4) subject is lost to follow-up. When possible, the Investigator should report the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin.)

Laboratory data analyses will include the following:

- Shift Analysis: Assessments of laboratory was based on classification of each measurement with reference to the normal ranges ("Low", "Normal" or "High"). Summary tables for each parameter tested providing the shift from Baseline (Derived) to End of Week 14 assessment will be provided by treatment group and visit.
- Quantitative Analysis: Summary statistics of results measurements and changes from Baseline (Derived) to End of Week 14 will be presented by treatment group and by visit. Note that quantitative results provided in database according to the cutoff values; e.g., '<0.13' the value of 0.13 will be used in the analysis. List of these cutoffs and related parameters will be provided.
- Incidence of Potential Clinically Significant (PCS): Incidence of post-baseline laboratory data of PCS will be summarized using descriptive statistics according to the cutoff's values detailed below.

Potentially Clinically Significant (PCS) Laboratory Values

Parameter	High/Low PCS
Alanine Aminotransferase (U/L)	**>3x ULN***
Aspartate Aminotransferase (U/L)	**>2x ULN***
Bilirubin (umol/L)	**>2x ULN***
Urea Nitrogen (mmol/L)	**>2x ULN***
Alkaline Phosphatase (U/L)	**>2x ULN***
Creatinine (umol/L)	**>1.5x ULN***
Creatinine Clearance (mL/min)	**<50**

* ULN – Upper Limit of age-sex matched normal range

20.3 ANALYSES OF VITAL SIGNS

Vitals signs will be measured at all visits except for Visit 3. Blood pressure and pulse will be recorded after resting supine for 5 minutes and standing after at least 3 minutes. Orthostatic hypotension (OH) is defined as a reduction of systolic blood pressure of at least 20 mmHg or 10 mmHg in diastolic blood pressure within 3 minutes of quiet standing. Height will be measured at screening only and weight will be measured at all visits. Orthostatic Hypotension Clinical Evaluation was also been conducted as described below:

1. On baseline and visits 4, 5 and 6, subjects that have OH will be asked to answer one question of the orthostatic hypotension activity scale (OHAS) which inquiries about dizziness, lightheadedness, feeling faint or feeling as though you might pass out. The answer is a scale from 0 to 10 where 0 is none and 10 is the worst possible.
2. Change in the differences in systolic and diastolic blood pressure measured during supine and standing positions.

Analyses of vital signs will be performed as described below:

- Summary statistics of results measurements and changes from Baseline (Derived) to each scheduled visit will be presented by treatment group and by visit in which measurement was taken.
- Proportion (%) of subjects with orthostatic hypotension at each scheduled visit and at any time following first study drug dose (see Definition of Date of First Study Drug Treatment) will be presented by treatment group. The denominator for this analysis will by all subjects included in the ST Analysis Set.
- Proportion (%) of subjects with clinically significant orthostatic hypotension following first study drug dose (see Definition of Date of First Study Drug Treatment) will be presented by treatment group. The denominator for this analysis will by all subjects included in the ST Analysis Set.
- Incidence and listing of measurements of Potential Clinical Significance (PCS) value after first study dose will be presented by treatment group. The denominator for this analysis will by all subjects included in the ST Analysis Set with post-baseline measurements.

Potentially Clinically Significant (PCS) Vital Signs Ranges

Parameter	Criteria for Potentially Clinically Significant*
Heart Rate (bpm)	≥120 and Increase ≥30
	≤50 and Decrease ≥30
Systolic** BP (mmHg)	≥160 and Increase ≥30
	≤80 and Decrease ≥30
Diastolic** BP (mmHg)	≥100 and Increase ≥20
	≤50 and Decrease ≥20

*** Increases / Decreases relative to Baseline (Derived) measurement**
**** For both measurements taken at supine and at standing**

20.4 ANALYSES OF ELECTROCARDIOGRAMS (ECG)

A standard 12-lead ECG will be performed at Screening, Baseline and Week 14/ETT. Additional ECGs will be performed if clinically indicated. ECGs will be conducted after approximately 5 minutes supine or recumbent rest using a standard ECG machine equipped with computer-based interval measurements.

The Investigator is responsible for evaluating the ECG interpretation in relationship to clinical signs and symptoms and reaching a medical decision regarding the subject's medical status. The ECG findings should be assessed by the Investigator as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS), as appropriate. All abnormalities, whether assessed as clinically significant or not, will be recorded. The ECG tracing should be initiated and dated by the Investigator.

Analyses of ECG evaluations will be performed in the following manner:

- Descriptive statistics of quantitative 12-Lead ECG parameters measured at scheduled visits by treatment group will be provided along with changes from baseline.
- Proportion (%) of subjects with abnormal ECG at each scheduled visit and at any time following first study drug dose (see Definition of Date of First Study Drug Treatment) will be presented by treatment group. The denominator for this analysis will be all subjects included in the ST Analysis Set.
- Proportion (%) of subjects with clinically significant abnormal ECG following first study drug dose (see Definition of Date of First Study Drug Treatment) will be presented by treatment group. The denominator for this analysis will be all subjects included in the ST Analysis Set.
- Shift analysis of Investigator assessment from Baseline (Derived) to each scheduled visit and to last observed assessment will also be performed.

- Incidence and listings of individual subject's ECG findings of Potential Clinical Significance (PCS) will be provided. The denominator for this analysis will be all subjects included in the ST Analysis Set.

Potentially Clinically Significant ECG Ranges

Parameter	Criteria for Potentially Clinically Significant (PCS)
QTcF interval (msec)	**Prolonged QTcF interval (QTcF >450)**
Heart Rate (bpm)	**Tachycardia (HR >120)** **Bradycardia (HR <50)**
PR interval (msec)	**Prolonged PR (PR>200)** **Short PR (PR<120)**
QRS Interval (msec)	**Wide QRS (QRS>120)** **Narrow QRS (QRS<70)**
RR Interval (msec)	**Short RR interval (RR<500)** **Long RR interval (RR>1200)**

20.5 ANALYSES OF PHYSICAL EXAMINATION

A complete physical exam (consisting of a review of all body systems) and neurological exam (including evaluation of mental status; motor function; balance and coordination; sensory function; reflexes and cranial nerves) at visit 1 will be conducted by the study neurologist (primary Investigator or sub-Investigator). On visit 7 and unscheduled visits a symptom-directed physical and neurological exam will be performed by the study neurologist.

The distribution of physical examination assessments at Baseline (Derived) and at the End of Week 14 according to protocol pre-defined body systems. The denominator will be the number of subjects of the ST Analysis Set.

Shift analysis from Baseline (Derived) to End of Week 14 for each body system will be performed. The denominator for this analysis will be the subjects of the ST Analysis Set.

Individual subjects' data listings providing all the physical assessments results will also be provided.

20.6 ANALYSES OF SUICIDALITY (COLUMBIA-SUICIDE SEVERITY RATING SCALE)

Suicidality analysis will use definitions outlined in Columbia-Suicide Severity Rating Scale (C-SSRS).

The distribution of the number of subjects identified with either "Suicidal behavior", "Suicidal Ideation" or "Suicidal Behavior or Ideation" at screening/baseline and during study will be provided.

Summary table, for each of the above classifications, displaying the shift from screening/baseline to the post baseline period, using the worst case scenario, will be provided displaying number and percentages of subjects in each category when broken down by treatment groups. The denominator for this analysis will be the number of subjects with baseline and post-baseline assessments.

Individual subjects' data listings providing the full questionnaire details will also be provided.

20.7 ANALYSES OF ORTHOSTATIC HYPERTENSION SYMPTOMS ASSESSMENT (OHSA) Q1

OHSA Q1 analysis will use definitions outlined in Orthostatic Hypotension Symptoms Assessment (OHSA) question 1.

Please note that the questionnaire was completed sporadically only by subjects experiencing orthostatic hypotension.

The distribution of no. of subjects by OHSA Q1 categorical score [=0 (no symptoms) or >0) will be provided by study period and by planned scheduled visits will be provided. The denominator for this analysis will be the number of subjects included in the ST Analysis Set.

A summary table, displaying the distribution of no. of subjects by OHSA Q1 Post Baseline Maximal Score will be displayed and individual subjects' data listings will also be provided.

20.8 TOLERABILITY AND DROP-OUT ASSESSMENTS

Tolerability analysis will be based on the number (%) of subjects who:

- Early terminated treatment.
- Early terminated study.
- Early terminated treatment due to adverse events.
- Early terminated study due to adverse events.

The denominator for this analysis will be the number of subjects included in the ITT Analysis Set.

Time to withdrawal will be presented by Kaplan-Meier curves broken down by treatment groups. Censoring of untreated subjects will use event day 0.

21 DEVIATION FROM STATISICAL ANALYSIS PLAN (SAP)

Any deviation from this Statistical Analysis Plan (SAP) will be reported in the Clinical Study Report.

END OF DOCUMENT