1 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 Number	P2B001/003
Version	3.0
Version Date	18 November 2020
Clinical Phase	Phase 3
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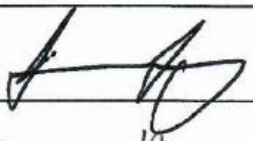
Sponsor: David S. Tierney M.D, CEO		Nov 11th 2020
PRA: PRA Health Science		Nov 13th 2020

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LIST OF ABBREVIATIONS

Abbreviation	Description
6-OHDA	6-hydroxydopamine
UPDRS ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Autoregressive
AUC	Area under the plasma concentration versus time curve
Bid	Twice per day
BP	Blood Pressure
CBC	Complete Blood Count
CGI-S	Clinical Global Impression - Severity
CGI-S	Clinical Global Impression - Improvement
CGR	Country or Geographical Region
Cmax	Maximum plasma concentration
CNS	Central Nervous System
CO	Complete Analysis Set
CR	Controlled Release
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CS	Compound Symmetry
CSH	Heterogeneous Compound Symmetry
CSSRS	Columbia Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMC	Eligibility Monitoring Committee
ER	Extended Release
ESS	Epworth Sleepiness Scale
EST	Early Study Termination
ETT	Early Treatment Termination
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
GDNF	Glial cell-line derived neurotrophic factor

Abbreviation	Description
DSMC	Data & safety Monitoring Committee
GI	Gastrointestinal
GLP	Good Laboratory Practice
H&Y	Hoehn and Yahr
HR	Heart Rate
hr(s)	Hour(s)
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent to Treat
k_{el}	Elimination rate constant
Kg	Kilogram
LCTM	Local Clinical Trial Manager
L-DOPA	Levodopa
LSM	Least Square Means
M	Meter
MAO	Mono Amine Oxidase
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
min	Minute or Minimum
mITT	Modified Intent to Treat
Ml	Milliliter
ML	Maximum-Likelihood
MMSE	Mini Mental State Exam
MPTP	(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Ms	Millisecond
N/A	Not Applicable
ºC	Degrees centigrade
PD	Parkinson's Disease
PDQ39	Parkinson's Disease Questionnaire 39
PI	Principle Investigator
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term

Abbreviation	Description
PPX	Pramipexole
QA	Quality Assurance
Qid	Four times per day
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale
RAF	Randomization Authorization Form
RAS	Rasagiline
REML	Restricted ML
RR	Respiratory Rate
RTSM	Randomization Trial Supply Management
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{½}$	Elimination half-life
TEAEs	Treatment Emergent Adverse Events
Tid	Three times daily
Tmax	Time at which Cmax occurs
TMF	Trial Master File
U	Unit
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale
WHO	World Health Organization

2 SYNOPSIS

Name of Sponsor/Company: Pharma Two B	
Name of Product: P2B001, Pramipexole 0.6 mg /Rasagiline 0.75 mg Once Daily (P2B001 0.6/0.75 mg)	
Name of Active Ingredient: Pramipexole, Rasagiline	
Title of study: 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.	
Study Sites: Approximately 70 sites in the United States, Canada, and Europe will be participating in the study.	
Planned Study Duration 16 – 22 months from first patient in until database lock. Planned first patient in: December 2017	**Development Phase:** Phase 3

<u>Objectives:</u>

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).

Secondary objectives:

- 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.
- To determine the efficacy of P2B001 0.6/0.75 mg as compared to its individual components in the change of Total PDQ39 score.
- 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.
- 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.
- 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).

Exploratory objective:

- 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).

- 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 $\leq$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) question 1.

- 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).

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.

Adverse events, vital signs and other safety data will be followed up by an independent Data and Safety Monitoring Board (DSMB).

Study Design:

This study is a phase 3, twelve-week, multi-center, multinational, randomized, double-blind, double-dummy, parallel group study.

Up to 525 eligible subjects with early untreated Parkinson's disease (PD) who are not early terminated from the study during screening or baseline visits and are randomized to treatment with P2B001 once daily (pramipexole 0.6 mg / rasagiline 0.75 mg), or pramipexole 0.6 mg once daily (PPX 0.6), or rasagiline 0.75 mg once daily (RAS 0.75), or pramipexole ER titrated to optimal dose (1.5, 3.0 or 4.5mg) using a randomization scheme of 2:2:2:1, respectively.

Each subject will be asked to take one capsule and 1-3 tablets once daily. The capsules will contain either P2B001 0.6/0.75mg or pramipexole 0.6 mg or rasagiline 0.75 mg or matching placebo. The tablets will contain either pramipexole ER 0.375 mg or pramipexole ER 1.5 mg or matching placebo.

Dosing Regimen:

- P2B001 pramipexole dihydrochloride 0.6 mg/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.

Study Structure:

- Up-titration phase
- Maintenance phase
- Down-titration phase
- Safety follow-up 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.

Study visits for the titration phase:

Subjects will be required to visit the clinic at the end of week 3 for a titration evaluation to assess the subject's satisfaction with and tolerance to the 1.5 mg dose of pramipexole ER (or placebo). At this visit, the PI or sub-Investigator may choose to keep the subject at 1.5 mg or increase the dose to 3.0 mg. Other study activities at this visit include assessment of CSSRS and QUIP-RS and review of adverse events and concomitant medications.

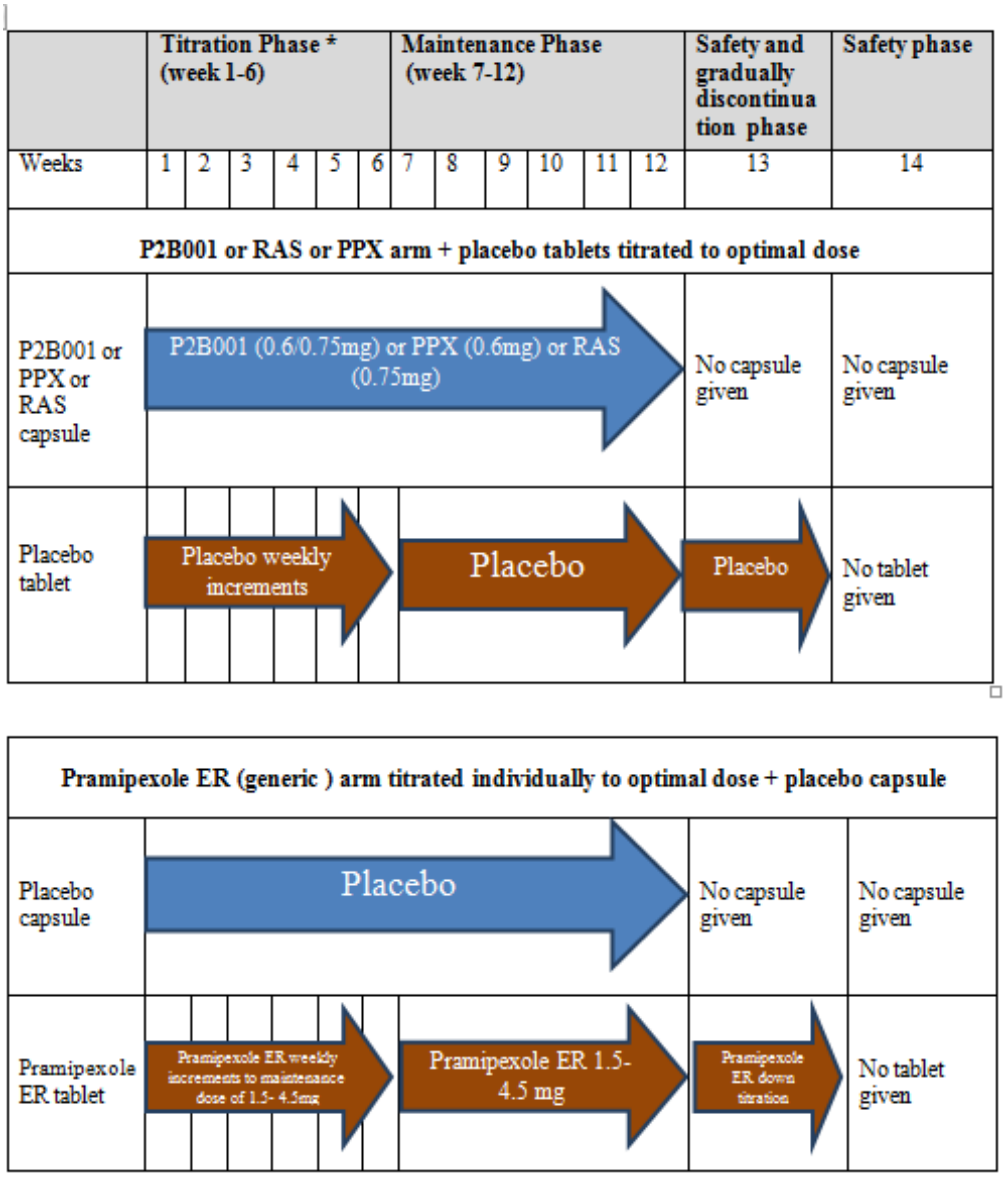
At the end of week 4 a phone call to the subject will be conducted by the PI or sub-Investigator to assess the subject's satisfaction with and tolerance to pramipexole ER (or matching placebo) and the possible need for increase of the dose. If the PI or sub-Investigator deem necessary, an unscheduled visit for a titration evaluation may be conducted at this time. At the end of week 5 the subject will be required to visit the clinic for a full study visit. In addition to scheduled study activities, the dose of pramipexole ER (or matching placebo) will be evaluated again to assess the subject's satisfaction and tolerability. As per the PI's or sub-Investigator's instructions, the dose may remain at 4.5 mg or decreased back to 3.0 mg or even to 1.5 mg if necessary. Following the end of week 6 no changes in dose are allowed. This will be deemed the maintenance dose of pramipexole ER or matching placebo tablets for the rest of the study. During all of this time the subjects will also take 1 capsule of P2B001/RAS 0.75/PPX0.6/Placebo which do not need titration.

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.

Down-titration phase: 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). No treatment with a once daily P2B001/RAS 0.75/PPX0.6/Placebo capsule during this time.

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.

Study design scheme:



*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 as 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.

Study activities:

Subjects will undergo visit specific study activities at screening, baseline, end of weeks 3, 4, 5, 8, 12/Treatment Termination and a safety follow up at end of week 14 (see Appendix 1, schedule of activities).

UPDRS II +III and ESS assessments will be conducted at the baseline visit, as well as end of weeks 5, 8, and 12/Treatment Termination. UPDRS III will also be conducted at screening.

QUIP-RS will be conducted at the baseline visit, as well as end of weeks 3, 5, 8, 12/Treatment Termination and week 14. CSSRS will be conducted at every study visit.

PDQ39, CGI-S and HRQOL SF-12 v 2 scales will be conducted at baseline and end of week 12/Treatment Termination.

CGI-I will be performed at end of weeks 5, 8 and 12/Treatment Termination visits. OSHA question 1 will be completed at baseline and end of weeks 5, 8 and 12/Treatment Termination, only for subjects experiencing orthostatic hypotension.

Subjects will take study medications (capsule and tablets) by mouth with a glass of water (8oz or 240ml). Study medications can be taken with or without food and efforts should be made to take the study medications at the same time every day.

To preserve the blind the capsules of once daily P2B001/RAS 0.75/PPX0.6/Placebo will be visually identical. The tablets of the pramipexole ER and their placebos will be visually identical.

Number of subjects:

Up to 525 eligible subjects with early untreated Parkinson's disease (PD) who are not early terminated from the study during screening or baseline visits and 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.

Diagnosis and Criteria for Eligibility:

Inclusion Criteria

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 postmenopaused. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

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 (see section 10.2).
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 moderate or severe 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.
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 eligibility monitoring committee (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.

Test product:

a. P2B001 pramipexole dihydrochloride 0.6 mg/rasagiline 0.75 mg Once Daily.

Reference therapy:

b. Pramipexole dihydrochloride 0.6 mg Once Daily.

c. Rasagiline 0.75 mg Once Daily.

Calibration arm:

d. Pramipexole ER titrated to optimal dose (1.5, 3.0 or 4.5mg) Once Daily

Duration of treatment:

Subjects will receive study drug or matching placebo treatment for a total of 12 weeks followed by a 7-day gradual discontinuation of treatment of pramipexole ER arm or matching placebo).

Statistical Methodology:

This study is a phase 3, twelve-week, multi-center, multinational, randomized, double-blind, double-dummy, parallel group study. Up to 525 eligible subjects with early untreated Parkinson's disease (PD) who are not early terminated from the study during screening or baseline visits and are randomized to treatment with P2B001 0.6/0.75 (150 subjects), or pramipexole 0.6 mg once daily (150 subjects), or rasagiline 0.75 mg once daily (150 subjects), or pramipexole ER titrated to therapeutic optimal dose (75 subjects) 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 PI and the central EMC.

This study is powered to demonstrate the superiority of (i) P2B001 0.6/0.75mg as compared to its individual components in the change from baseline to Week 12/Treatment Termination in Total UPDRS score and, (ii) to demonstrate the superiority of P2B001 0.6/0.75mg over pramipexole ER in the change from baseline to Week 12/Treatment Termination in the ESS.

Treatment with pramipexole ER will serve as a calibration arm to better characterize P2B001 against currently used therapy. Therefore, with the exception of change from baseline to Week 12/Treatment Termination in the ESS, only descriptive statistics and no formal significance testing will be made between the pramipexole ER arm and the other three study arms.

Week 12/Treatment Termination is defined for all statistical analyses involving significance as the last visit in which a subject was treated with the study drug.

Sample Size Rational:

The study was powered to allow achieving two goals:

- 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 5, 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 5 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 to be included in each P2B001 0.6/0.75mg arm, rasagiline 0.75mg arm and pramipexole 0.6mg arm 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.

- 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 to be included in the P2B001 0.6/0.75mg arm and 75 subjects to be included in pramipexole ER arm, 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%.

Sample Size Re-Assessment:

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 protocol amendment.

Randomization:

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.

Overall Significance Level and Multiplicity Adjustment:

The overall significance level for this study will be 5% using two-tailed tests. No interim analyses or futility analyses are planned for this study.

The overall, experiment-wise type-I error rate of 5% will be preserved according to the below plan:

1. The principal analysis of the primary endpoint is designed to demonstrate the efficacy of P2B001 0.6/0.75mg as compared to its individual components in the changes from baseline to Week 12/Treatment Termination. Accordingly, analysis will employ two contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily. The type-I error of 5% for multiple contrasts testing for the primary endpoint will be preserved by determining that the primary endpoint is met only if both comparisons will favor P2B001 0.6/0.75mg at a two-tailed alpha level of 5% each.
2. Multiplicity adjustment for multiple endpoints testing for the secondary endpoints will utilize the gate keeping hierarchical method according to the following order and plan:
   - For the 1st secondary endpoint, namely, the P2B001 0.6/0.75mg vs. pramipexole ER contrast in the change from baseline to Week 12/Treatment Termination in the ESS, will be considered as met only if both primary endpoint contrasts as above defined and the P2B001 0.6/0.75mg vs. pramipexole ER contrast in the change from baseline to Week 12/Treatment Termination in the ESS will all be met (total of 3 contrasts) at a two-tailed alpha level of 5% each.

- The 2nd secondary endpoint, namely, the change from baseline to Week 12/Treatment Termination visit in the Total PDQ39 will be considered as met if all of the 3 previous tested contrasts (primary endpoint and 1st secondary endpoint) as well the two contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 2nd secondary endpoint will all be met (total of 5 contrasts) at a two-tailed alpha level of 5% each.
- The 3rd secondary endpoint, namely, the change from baseline to Week 12/Treatment Termination visit in the ADL UPDRS (part II) score will be considered as met if all of the 5 previous tested contrasts (primary endpoint, 1st and 2nd secondary endpoints) as well the two contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 3rd secondary endpoint will all be met (total of 7 contrasts) at a two-tailed alpha level of 5% each.
- The 4th secondary endpoint, namely, the change from baseline to Week 12/Treatment Termination visit in the motor UPDRS (part III) score will be considered as met if all of the 7 previous tested contrasts (primary endpoint, 1st, 2nd and 3rd secondary endpoints) as well the two contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 4th secondary endpoint will all be met (total of 9 contrasts) at a two-tailed alpha level of 5% each.
- The 5th secondary endpoint, namely, the CGI-S responder's analysis at Week 12/Treatment Termination visit (change from baseline ≥1 CGI-S points) will be considered as met if all of the 9 previous tested contrasts (primary endpoint, 1st, 2nd, 3rd and 4th secondary endpoints) as well the two contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 4th secondary endpoint will all be met (total of 11 contrasts) at a two-tailed alpha level of 5% each.

Principal Analysis of the Primary Endpoint:

The primary efficacy endpoint for this study is the change from baseline to Week 12/Treatment Termination in total UPDRS score (defined as sum of parts II and III, scores (0-160). The statistical model will be a Mixed Model for Repeated Measures (MMRM) (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical week in trial by treatment interaction, country or geographical region (CGR), and baseline 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 changes form baseline to post-baseline visits (weeks 5, 8 and 12) collected from all subjects randomized into the study will be used as response in the model. The differences between the P2B001 0.6/0.75mg arm as compared to its 2 individual components at Week 12/Treatment Termination will be estimated and tested using 2 contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg and, P2B001

0.6/0.75mg vs. rasagiline 0.75mg. The study primary endpoint will be considered as met only if both contrasts will favor P2B001 0.6/0.75mg at a two-tailed alpha level of 5% each.

Statistical Analysis Plan (SAP)

A more detailed SAP will be developed while the study is ongoing and prior to locking the database and un-blinding.

If ever there is a discrepancy in the between the Protocol and the Statistical Analysis Plan, the methods defined in the SAP will have precedence.

3 INTRODUCTION

3.1 Background

Parkinson's disease (PD) is an age-related neurodegenerative disorder. The major motor symptoms include rigidity, tremor, and bradykinesia. Levodopa (L-DOPA) provides meaningful benefit for most patients, particularly in the early stages of the disease. However, chronic L-DOPA treatment is associated with the development of motor complications (motor fluctuations and dyskinesia) in the majority of individuals. Further, levodopa induced off time and dyskinesia are dose-related and seen with higher doses of L-DOPA (Olanow CW M. F., 2013) . To delay the introduction of L-DOPA and to permit the use of lower doses, many physicians choose to initiate therapy with a monoamine oxidase Type B (MAO-B) inhibitor, frequently rasagiline, a dopamine agonist, commonly pramipexole, or both (often in sequential order). The use of these treatments prior to the introduction of L-DOPA can provide satisfactory clinical control in the early stages of the disease, enable lower doses of L-DOPA to be used when it is required and delay developing L-DOPA associated motor complications.

Pramipexole is a non-ergot, specific and selective dopamine receptor agonist of the dopamine D2 subfamily (Perez-Lloret S, 2010). Rasagiline is a selective and irreversible monoamine oxidase B (MAO-B) inhibitor (Youdim MB, 2001) . Thus, while pramipexole compensates for the lack of endogenous neurotransmitters by activating the postsynaptic dopamine receptor, rasagiline causes an enhancement of synaptic dopamine levels by inhibiting dopamine oxidative metabolism.

Pramipexole has been shown to possess neurotropic activity in animal models (Imamura K, 2008) (Li C, 2010). In the last decade, studies of rasagiline have shown that it also works through additional anti apoptotic mechanisms (Wu Y, 2015), and neurotropic effects (Azilect EPAR) that may contribute to its anti-parkinsonian benefit. Therefore, further compatibility of the mechanisms of these two agents may exist.

While the use of alternative treatment prior to introduction of L-DOPA is now an acceptable approach (Olanow W, 2009), approved therapeutic doses of pramipexole and rasagiline have potential safety concerns and therapeutic limitations. For example, therapeutic doses of dopamine agonists are typically associated with nausea, vomiting, constipation and orthostatic hypotension. Further, pramipexole is also associated with a risk of impulse control disorders, peripheral edema, psychosis and excessive daytime sleepiness, and a risk of sudden onset sleep episodes in unintended situations such as while driving. These side effects are more pronounced with higher dosages. Rasagiline is largely well tolerated but has limited efficacy and also has potential safety concerns, particularly with respect to the risk of a hypertensive crisis with foods that are high in tyramine and as serotonin syndrome particularly when employed in high doses or in combination with selective serotonin reuptake inhibitors and other anti-depressants that are commonly prescribed in Parkinson's disease. Again, higher doses are associated with a greater risk of developing these adverse effects.

Pharma Two B's therapeutic strategy is to develop a fixed-dose combination of low doses of agents with complementary mechanisms of action (ie, a dopamine agonist and a MAO-B inhibitor) in an attempt to obtain enhanced anti-Parkinsonian efficacy and a better safety profile in comparison to what can be achieved with higher doses of either agent alone, as the drugs are currently employed.
Pharma Two B has investigated the effects of combining low doses of pramipexole and rasagiline in both animal models and PD patients. Nonclinical data demonstrate that low doses of the MAO-B inhibitor rasagiline and the dopamine agonist pramipexole act synergistically with respect to behavioural effects and striatal dopamine.
In animal studies, administering both agents in a slow infusion over 24 hours (mimicking extended-release) further improves their efficacy, presumably by allowing the agents to work together for a longer time, enhancing their mutual action. The half-lives of the currently available pramipexole and rasagiline vary ($T_{1/2}$ is 8-12 hours for pramipexole, and 1.5-3.5 hours for rasagiline) (Wright CE, 1997) (Thebalut JJ, 2004). Therefore, the P2B001 combination comprises an extended release (ER) profile for both pramipexole and rasagiline, which enables release throughout the day for both drugs, allowing for a longer time of mutual action.

P2B001 is intended to offer a novel approach to PD treatment in that it would be:

- a fixed-dose combination of the two agents;
- an extended-release formulation of both pramipexole and rasagiline; and
- a new low-dose regimen of the two agents intended to maximize efficacy while limiting known adverse effects of approved higher doses of the individual components.

A Phase 2b clinical study (P2B001/001) in patients with early Parkinson's disease testing the low-dose combinations of pramipexole (0.3 or 0.6 mg) and rasagiline (0.75 mg) in an extended-release formulation has recently been completed and demonstrated that the combination provides highly significant and clinically meaningful benefits in comparison to placebo, with a good safety profile (Olanow CW K. K., 2017). The primary efficacy endpoint was the change from baseline to Week 12 in total UPDRS (I+II+III) score. The UPDRS data showed significant improvement at each time point relative to baseline ($p<0.0001$ at 4, 8, and 12 weeks) for both the 0.3/0.75 mg and 0.6/0.75 mg dose combinations. The placebo-subtracted differences were statistically significant at 12 weeks, these were -4.67 points for 0.6/0.75 mg ($p=0.0004$) and -3.84 points for 0.3/0.75 mg ($p=0.0027$).
Out of the two above tested doses, the 0.6/0.75 mg dose was selected for the phase III study. Although between-group differences in efficacy were not statistically significant, there was consistent numerical benefit for this dose on total, motor and ADL UPDRS scores, PDQ39 and CGI-severity.

3.2 Preclinical Pharmacology Studies

Several non-clinical pharmacology studies assessing the effects of the proposed drug combination have been conducted. When the combination of rasagiline and pramipexole were administered together at doses that individually produce only small changes in striatal dopamine levels in MPTP-lesioned animals, greater than additive recovery of dopamine levels were observed. Further, when the sustained-release dosage is mimicked, the effect is greater than when the same combination is administered as immediate release. This has been supported in a further study in which L-DOPA-induced contralateral turning and the stepping test in the 6-OHDA-lesioned rat model showed greater than additive changes when rasagiline and pramipexole were administered in combination.

3.3 Toxicology Studies

A review of the pharmacological profiles of pramipexole and rasagiline revealed that both products are highly specific in their activities. Rasagiline is highly specific for MAO-B (Lecht S, 2007). Similarly, pramipexole demonstrated specificity for D2-D3 dopamine receptors (Summary Basis of Approval NDA 20667., 1997). The nonclinical development programs for Mirapex and Azilect included full batteries of toxicity testing needed for approval of chronically administered drug products. These studies identified few end organs for toxicity other than those predicted by the pharmacology of the two substances. Toxicological interactions are not predicted by the available human and animal data.

In addition, evaluation of adverse effects in the LARGO and PRESTO studies showed no indication of an increase in dopaminergic adverse effects in patients when rasagiline was added to dopamine agonist treatment. Also, increases in adverse dopaminergic or other adverse effects have not been noted in clinical studies in which other MAO inhibitors (e.g., selegiline) have been used with pramipexole (Du F, 2005), (Hauser RA, 2010), (Rascol PB, 2010), (Hubble JP, 1995), (Shannon KM, 1997), (PSG, 1997), (Mirapex ER Label, 2010)

The P2B001/001 phase 2b study did not show any new or unexpected adverse events and showed a decrease in most dopaminergic adverse events.

3.4 Clinical Studies

Pharma Two B Ltd. has conducted three clinical trials with its low-dose, extended-release, fixed dose formulation of pramipexole and rasagiline for the treatment of early Parkinson's disease. The initial pharmacokinetic study (Study 10/10) was four arms, crossover, pharmacokinetic study in healthy, fasted young adults comparing immediate release rasagiline (Azilect®, 1 mg, commercial), ER pramipexole (Mirapex ER®, 0.75 mg, commercial), both commercial drugs taken together, and Pharma Two B's proprietary P2B001 containing doses of rasagiline (1 mg) and pramipexole (0.75 mg), both ER. Results indicated that no pharmacokinetic interactions occurred between the components when given together. The Cmax and AUC of each component

in the combination were either equal (in case of Pramipexole) or lower (in case of Rasagiline) compared to the Cmax and AUC of the drugs given alone, indicating that no safety issues resulting from increased exposure are expected. In this study, the availability of the drugs in the P2B001 is about 90% for pramipexole and about 80% for rasagiline relative to the commercial mono-therapies. Furthermore, both drugs were present in plasma throughout the day and the high peaks associated with the commercial products were avoided with P2B001. The second study has recently been completed. This was a phase 2b, twelve-week multi-center, randomized, double-blind, placebo-controlled, parallel group study, to determine the safety, tolerability and efficacy of two doses of P2B001 in subjects with early Parkinson's disease. The study tested two low-dose, fixed-dose combinations of P2B001, once-daily containing pramipexole and rasagiline (0.6 mg/0.75 mg and 0.3 mg/0.75 mg) relative to an identical placebo capsule. The results demonstrated robust statistically significant and clinically meaningful improvement results compared to placebo in Parkinson's disease symptoms with a favorable safety profile at two dosage strengths of the combination product. The primary efficacy endpoint was the change from baseline to Week 12 in total UPDRS (I+II+III) score. The UPDRS data showed significant improvement at each time point relative to baseline ($p<0.0001$ at 4, 8, and 12 weeks) for both the 0.3/0.75 mg and 0.6/0.75 mg dose combinations. The placebo-subtracted differences were statistically significant at 12 weeks, these were -4.67 points for 0.6/0.75 mg ($p=0.0004$) and -3.84 points for 0.3/0.75 mg (0.0027). Adverse events of frequency ≥ 5% are listed in the table below.

Common Adverse Events (Frequency ≥5%) (P2B001/001) Number and % of Subjects

	Placebo (N=50)	**P2B001 0.3/0.75** (N=50)	**P2B001 0.6/0.75** (N=49)
Diarrhea	3 (6%)	0 (0%)	0 (0%)
Nausea	1 (6%)	6 (12%)	10 (20.4%)
Fatigue	1 (2%)	1 (2%)	4 (8.2%)
Nasopharyngitis	5 (10%)	2 (4%)	2 (4.1%)
Dizziness	4 (8%)	2 (4%)	5 (10.2%)
Headache	4 (8%)	1 (2%)	1 (2%)
Somnolence	0 (0%)	4 (8%)	8 (16.3%)
Tremor	3 (6%)	3 (6%)	4 (8.2%)
Insomnia	2 (4%)	0 (0%)	3 (6.1%)
Orthostatic hypotension	4 (8%)	1 (2%)	2 (4.1%)

As for severity, most of the adverse events (frequency ≥5%) were mild. Interestingly most of the somnolence reported for the 0.6/0.75 mg dose were mild (67%) while for the 0.3/0.75 mg dose most were moderate. A second pharmacokinetic study (Study P2B001/002a) was recently completed in healthy male and non-pregnant female volunteers, comparing the effect of food (high-fat meal versus fasting) on the bioavailability of pramipexole and rasagiline from a single oral dose of P2B001 Pramipexole/Rasagiline 0.6 mg/0.75 mg once daily capsule. Results indicated that food does not alter the peak or extent of absorption of both pramipexole and rasagiline from P2B001.

3.5 Summary of Non-Clinical and Clinical Studies

P2B001 is an oral fixed-dose, extended release product that combines pramipexole and rasagiline for the treatment of early Parkinson's disease. The Pharma Two B product is novel in that it would be:

- A fixed-dose combination of the two agents.
- A low-dose regimen intended to maximize efficacy while limiting adverse effects.
- The first product incorporating a extended release formulation of rasagiline.

Pharma Two B Ltd. has completed several studies characterizing P2B001 in a rodent model of PD, a phase 1 study with healthy volunteers and a phase 2b study with early PD patients, all demonstrated the therapeutic advantage of Pharma Two B's proprietary extended release combination:

- The nonclinical studies in rodents PD models suggest a therapeutic advantage of combining low doses of rasagiline and pramipexole and suggest further improvement when both are administered in a sustained fashion.
- The Phase 1 study (Study 10/10) indicates the absence of a pharmacokinetic interaction between pramipexole and rasagiline when co-administered. Further, when administered at equivalent doses, the plasma profile of pramipexole from Pharma Two B's extended release combination product mirrors that of Mirapex ER®. The plasma profile from Pharma Two B's extended-release combination product differs markedly, as expected, in Cmax from that of immediate-release Azilect, but provides similar exposure.
- The 12-week Phase 2B, multi-center, randomized, double-blind, placebo-controlled, parallel group study of P2B001 in subjects with early Parkinson's disease (study P2B001/001) demonstrated statistically significant and clinically meaningful improvement compared to placebo in Parkinson's disease symptoms with a favorable safety profile at two dosage strengths of the combination product (0.6 mg pramipexole/0.75 mg rasagiline and 0.3 mg pramipexole/0.75 mg rasagiline).

P2B001 at dose of 0.6 mg pramipexole/0.75 mg rasagiline will be used for further development of Pharma Two B's product.

4 STUDY OBJECTIVES

Pharma Two B intends to show that:

- P2B001 has superior efficacy as compared to each of its components.
- P2B001 is safe and tolerable.
- P2B001 has descriptively comparable efficacy as well as safety benefits as compared to pramipexole ER.

4.1 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).

4.2 Secondary Objectives

- 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.
- To determine the efficacy of P2B001 0.6/0.75 mg as compared to its individual components in the change of Total PDQ39 score.
- 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.
- 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.
- 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).

4.3 Exploratory Objectives:

- 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).

- 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.

- 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.

4.4 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.

5 INVESTIGATIONAL PRODUCT

The drug combination P2B001 is comprised of two drugs; pramipexole and rasagiline, both currently approved drugs and routinely used in standard therapy for early PD. Each active pharmaceutical ingredient (API) is formulated separately as extended-release pellets (i.e., inert sugar bead core layered with drug and covered with an extended release coating). The two types of pellets are packed into a capsule to provide the desired dose.

Pramipexole is a non-ergot, specific and selective dopamine receptor agonist of the dopamine D2 subfamily (Perez-Lloret S, 2010), currently marketed as immediate release and as extended release. Rasagiline is a selective and irreversible monoamine oxidase B (MAO-B) inhibitor (Youdim MB, 2001). Thus, while pramipexole compensates for the lack of endogenous neurotransmitters by activating the postsynaptic dopamine receptor, rasagiline causes an enhancement of synaptic dopamine levels by inhibiting dopamine oxidative metabolism.

Pramipexole is currently marketed as immediate release and as extended release (ER). In this study the ER product will be used as a calibration arm. The starting dose of pramipexole ER is 0.375 mg given once per day. Based on efficacy and tolerability, dosages may be increased gradually, not more frequently than every 5 to 7 days, first to 0.75 mg per day and then by 0.75

mg increments up to a maximum recommended dose of 4.5 mg per day (Summary Basis of Approval NDA 20667., 1997).

Rasagiline is only marketed as immediate release. The recommended monotherapy dose of rasagiline is 1 mg once daily (Azilect Label, 2010).

5.1 Dosage

The dosage for the three main study arms will be:

- P2B001 (pramipexole dihydrochloride 0.6 mg/rasagiline 0.75 mg) once daily
- Pramipexole dihydrochloride (0.6 mg) once daily
- Rasagiline (0.75 mg) once daily

The dosage for the calibration arm will be:

- Pramipexole ER individually titrated to an optimal dose (1.5-4.5mg/day).

The combination product (P2B001) and its individual components, pramipexole and rasagiline were produced by: Catalent Pharma solutions Somerset, USA address: 14 Schoolhouse Rd. Somerset, NJ 08873, USA.

The pramipexole ER comparator and its placebo tablets were produced by:
Dr. Reddy's Laboratories Limited, FTO UNIT 3, Survey No 41 Bachupally village, Qutubullapur Mandal Ranga Reddy District Telangana 500090 India

5.2 Dose Modification

Subjects may be allowed to miss a dose of study medication if:
1) Subject develops an adverse event that the Investigator believes requires the subject's dose to be held temporarily, or
2) Subject loses their kit of study medication and a replacement kit is requested, in this situation the PI should request an emergency shipment to alert the distributor to ship the replacement kit urgently).
During the pramipexole ER titration phase, the PI or sub-Investigator may modify (up or down) subject's dose to either1.5, 3.0 or 4.5 mg of the pramipexole ER/identical placebo to reach the optimal tolerated therapeutic dose. Following the titration phase, after week 6, no modifications are allowed.
If the subject experiences intolerable adverse events, dosing may be held temporarily or withdrawn (all treatments, including both capsules and tablets, please note that pramipexole

ER/matching placebo tablets need to be down titrated gradually (see down titration instructions in section 6.1). However, the subject will continue to be followed-up according to the protocol pre-planned schedule of activities
No other dose modifications will be allowed in this study.

5.3 Method of Administration & Meals

Subjects will take the study medications (capsule and tablets) by mouth with a glass of water (8oz or 240ml). Study medication can be taken with or without food and efforts should be made to take the study medication at about the same time every day.

6 STUDY DESIGN

6.1 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.

Up to 525 eligible subjects with early untreated PD, who are not early terminated from the study during screening or baseline visits and 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 PI and the central EMC. Subjects will be recruited from approximately 70 sites in North America and Europe.

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.

Dosing Regimen:

- 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.

Study Structure:

- Up-titration phase
- Maintenance phase
- Down-titration phase
- Safety follow-up phase.

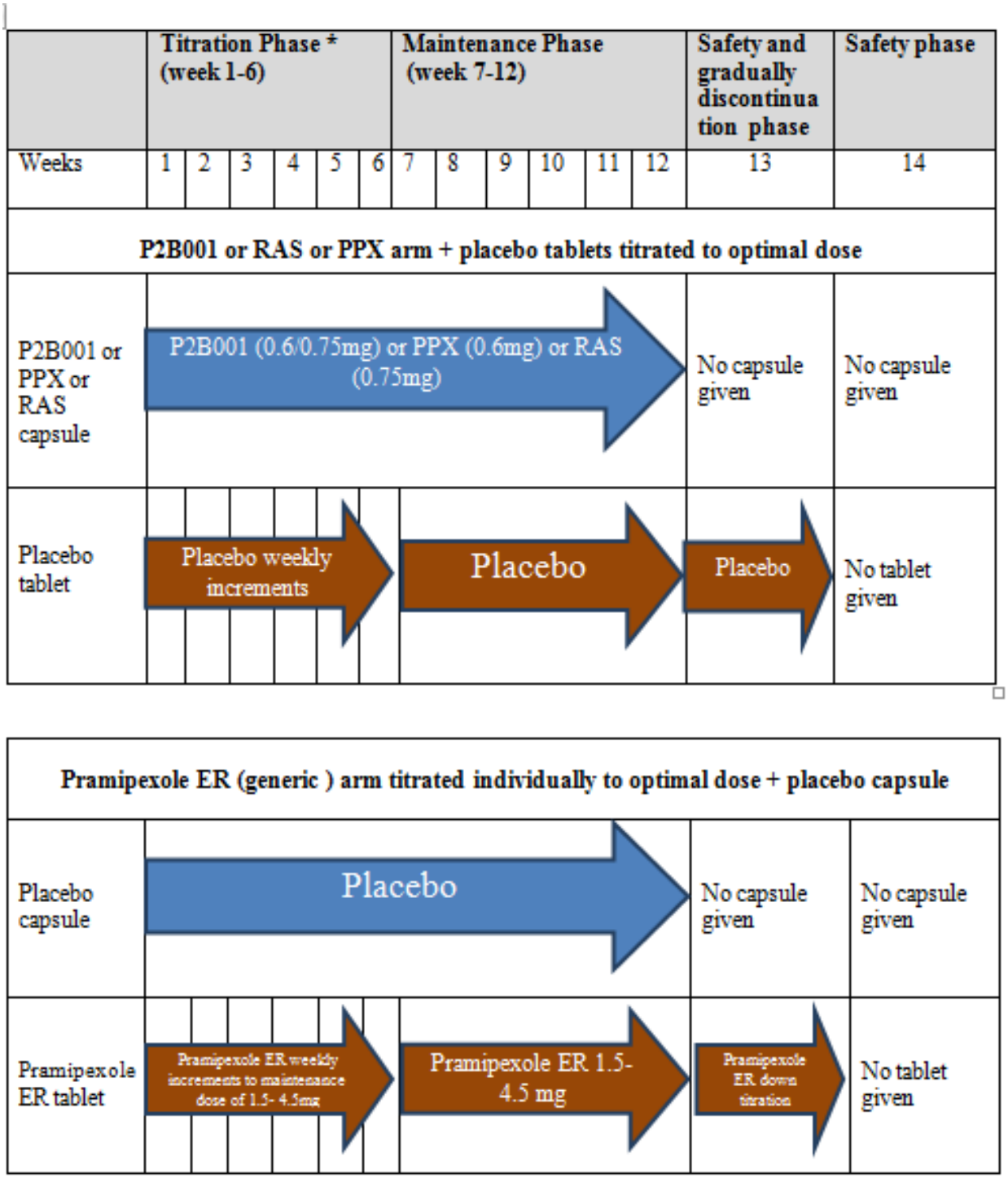
Up-Titration phase: A 3-6 week double blind, double dummy titration phase with pramipexole ER or matching placebo. During this phase subjects will also take 1 capsule of P2B001/RAS 0.75/PPX0.6/Placebo which does not need titration. For the first 3 weeks the titration of the pramipexole ER will be increased 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.

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.

Down-titration phase: 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.

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.

Study design scheme:



*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.

6.2 Rationale for Study Design, study population and Doses

The study is designed to show the contribution of both active components, pramipexole and rasagiline, to the efficacy of the combination product P2B001 by comparing the efficacy between P2B001 and its individual components as the co-primary objectives. In addition, the study includes a calibration arm in order to characterize the benefits of P2B001 in respect to safety and efficacy of currently used therapeutic doses of pramipexole ER.

Early Parkinson's disease patients are chosen for this study, since they are the patient population that most likely can benefit from the combination product. The use of the combination product can delay the beginning of treatment with L-DOPA and as consequence reduce and delay the risk of developing motor complications with L-DOPA treatment.

The study was adequately powered to allow demonstration of the efficacy of P2B001 over its 2 components by randomly allocating 150 subjects to each of P2B001 arms and its 2 components. Additional 75 subjects will also be randomized to treatment with pramipexole ER to allow characterization of the benefits of P2B001 with reference to pramipexole ER titrated to individual optimal doses.
The dose of P2B001 chosen for this study is based on the results of the previous phase 2b dose ranging study (P2B001/001). Both doses of P2B001 that were tested (0.6 mg pramipexole/0.75 mg rasagiline and 0.3 mg pramipexole/0.75 mg rasagiline) provided significant clinical benefits with a good safety profile. The 0.6 mg pramipexole/0.75 mg rasagiline dose was chosen because there was consistent numerical benefit for this dose on total, motor and ADL UPDRS scores, PDQ39 and CGI-severity assessments. Both doses were well tolerated with an adverse event profile similar to placebo, with the exception of somnolence and mild nausea, known adverse events of pramipexole. Slightly more cases of somnolence and nausea were reported for the 0.6 mg pramipexole/0.75 mg rasagiline dose, but both doses did not show statistically significant differences from placebo in the ESS scale and the reports of nausea in both doses were mostly mild and transient.

Subjects with mild to moderate renal impairment and subjects with mild hepatic impairment were included in the previous phase 2b study and were followed up with monthly renal and liver function tests to assure compliance with exclusion criteria 17 and 18 and these showed no significant changes. In the current study subjects with mild renal and or mild hepatic impairment will also be included with the same additional follow up to assure compliance with exclusion criteria 17 and 18. In case of worsening in a subject's liver or renal condition and the subject is not compliant with the above exclusion criteria, their participation in the study will be stopped.

Subjects with moderate renal impairment (creatinine clearance between 30 and 50 mL/min) will be excluded in the current study due to possible titration of pramipexole ER tablets to doses above the recommended dose in such patient populations, which is 2.25mg/day.

7 STUDY POPULATION

7.1 Number of Subjects

Study population includes 525 eligible early stage untreated PD patients who are not early terminated from the study during screening or baseline visits. Subject will be recruited from approximately 70 sites in North America and Europe.

7.2 Subjects Enrolment

All subjects enrolled must be eligible as per Inclusion/Exclusion Criteria. Personal interview including medical history, physical and neurological examination, and evaluation for trial eligibility will be done as specified in Schedule of Activities, Appendix I.

7.3 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.

7.4 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 (see section 10.2).

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.

7.5 Early Discontinuation Subjects

A subject can leave the study at any time for any reason without consequences, upon request. The protocol distinguishes between two types of early Terminations:

- Early Treatment Termination (ETT)
- Early Study Termination (EST)

Early Treatment Termination (ETT)

A subject who discontinued study medication for any reason before the end of week 12 will continue pre-planned study schedule of activities as follow up. The subject will be requested to undergo a treatment termination visit as described in section 9.2.11

Please note that P2B001/PPX 0.6/RAS 0.75/Placebo capsules can be stopped immediately, while pramipexole ER/matching placebo tablets need to be gradually down titrated as described in section 6.1.

The reasons for withdrawal could include the following:

- Subject withdrawal of consent to be treated with study medication(s) but still consenting to participate in study visits and activities
- Request of the Investigator for any medical or other reason
- Request of the primary care physician via the Investigator
- Pregnancy
- Non-compliance
- Subject who cannot achieve the minimum therapeutic dose of pramipexole ER (or placebo) of 1.5 mg per day.
- Major protocol violation
- Adverse Event/Experience
- Lack of Efficacy
- Subjects who, according to the Investigator, need additional therapy that is excluded in the protocol for the treatment of the disease.
- Any other reason relating to the patient's safety or integrity of the study data.

If a subject suspect that she is pregnant, a urine test will be performed at the site. If the urine test is positive, study drug administration will be interrupted pending the results of a confirmatory blood/serum test. If the pregnancy is confirmed with a positive blood/serum test, then the subject will be permanently discontinued from study drug, but should participate in a Treatment Termination visit and continue with all the study visits as follow up visits up to and including safety follow up visit at week 14. The PI will follow the subject until she has given birth.

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.

Early Study Termination (EST)

A subject who requests to stop study participation for any reason before the end of week 12, including study treatment and study scheduled activities, will be requested to undergo a study termination visit as described in section 9.2.11, unless erroneously randomized or withdrew consent prior to first dose.

The reasons for EST could include the following:

- Pregnancy
- Adverse Event/Experience

- Subject withdrawal of consent and refusal to continue participation in study due to lack of efficacy or due to other reasons
- Lost to follow-up/failure to return
- Death
- Erroneously randomized
- Withdrew consent prior to first dose

If there is a medical reason for withdrawal and the subject refuses to come to study visits after study medication was stopped, the subject will remain under the supervision of the PI as long as the PI deems medically necessary.

7.6 Subject Replacement

A subject who leaves the study at any time for any reason will not be replaced.

8 ASSESSMENTS

8.1 Schedule of Activities

See Appendix I for a table describing activities performed at each visit.

8.2 Evaluation of Pramipexole ER (or Placebo) Dose

The subject will be required to visit the clinic at the end of week 3 and 5 (visit 3 and 4) and be available for a phone call at the end of week 4 for titration evaluation; to assess the tolerability and efficacy of the pramipexole ER (or placebo) and the possible need for changing the pramipexole ER dose.

8.3 Safety and Tolerability

8.3.1 Physical and Neurological Exams

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.

8.3.2 Safety Laboratory Tests – see Appendix II

Hematology, chemistry and urinalysis tests will be performed as general measures of health. Eurofins Scientific will be responsible for shipment, storage, and testing of all laboratory samples. Instructions will be included in the laboratory manual.

8.3.3 ECG

12-lead ECGs will be performed to evaluate the cardiovascular system on the screening and baseline visits and on visit 7.

8.3.4 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 is defined as a reduction of systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure within 3 minutes of quiet standing (Aronow WS, 2011). Height will be measured at screening only and weight will be measured at all visits.

8.3.4.1 Orthostatic Hypotension Evaluation

1. On baseline and visits 4, 5 and 6, subjects that have OH according to the description above (section 8.3.4) will be asked to answer one question of the orthostatic hypotension activity scale (OHAS) which inquires 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.

8.3.5 Concomitant Medications

Concomitant medication logs will be completed at the Screening visit and will be updated at each subsequent visit. The logs will include the medication taken by the subject over the past 3 months. A separate log will record anti-PD medications that were previously used.

8.3.6 Adverse Events

Adverse events will be recorded after the signing of the informed consent of enrolled subjects throughout the study and shall be reviewed and updated at each subsequent visit and during any phone contact with the subject. AEs for screen failure subjects will be captured only in the source documents and not in the eCRF.

8.3.7 Sleepiness

Sleepiness will be evaluated at baseline and at end of weeks 5, 8 and 12/Treatment Termination visit (visits 4, 5 and 6) using the Epworth Sleepiness Scale (ESS, see Appendix III).

8.3.8 Impulsive-Compulsive Disorders

The questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, (QUIP-Rating Scale Appendix VI), will be used on the 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.

8.3.9 Suicidality

Columbia Suicide Severity Rating Scale (CSSRS, see Appendix VIII) will be used. Baseline / screening version of the CSSRS will be used at screening visit. This version assesses suicidality in a patient's lifetime and during the past six months. The Since Last Visit (SLV) version of the CSSRS will be used at all consequent visits. This version assesses suicidality since the patient's last visit. Efforts must be made to ensure that the same trained team member completes this questionnaire for each subject.
A subject with any suicidal ideation that answered YES to questions 4 or 5 in the CSSRS questionnaire will be referred to a mental health professional.
CSSRS-SLV will be used on the 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).

8.4 Efficacy

Efforts must be made to ensure that the same Investigator completes the UPDRS, CGI-S and CGI-I scales at all visits that these scales are done.

8.4.1 UPDRS – see Appendix IX

The UPDRS assesses motor and functional abilities of the subjects. The total UPDRS is defined for this study as the sum of Parts II and III (Activities of Daily Living and Motor sections). These will be completed by history and examination. UPDRS II and III will be performed at baseline visit and at end of weeks 5, 8 and 12/Treatment Termination (visits 4, 5, and 6). UPDRS part III will be completed also at screening visit to support diagnosis and the score will be included in the RAF.
The UPDRS part III evaluation will be conducted by a trained neurologist or other senior trained research staff with at least 10 years' experience in conducting the UPDRS. All attempts will be made to ensure that the same trained research staff member performs the UPDRS part III at all visits for each subject and at approximately the same time of the day and time following administration of medication. The UPDRS part II will be completed by a trained neurologist or other trained research staff member as delegated by the Site PI. For consistency efforts must be made to ensure that the same trained research staff member will do the UPDRS part II at all required visits for all subjects.

8.4.2 Clinical Global Impression - severity (CGI-S) - Appendix IV

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. 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; or 7, extremely ill. Efforts must be made to ensure that the same neurologist performs the CGI-S at all visits.

8.4.3 Clinical Global Impression of Improvement (CGI-I) – Appendix XIV

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.
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; or 7, very much worse. Efforts must be made to ensure that the same neurologist performs the CGI-I at all visits.

8.4.4 Quality of Life PDQ39 – Appendix X

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): ever/occasionally/sometimes/often/always or cannot do at all.

8.4.5 Health-Related Quality of Life (HRQOL) SF-12v2 questionnaire – Appendix VII

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 Termination (visits 2, and 6).

8.5 Compliance

8.5.1 Study Compliance

At each study visit the Investigator and/or site coordinator will assess the subject's compliance with the prescribed regimen for the study medication using pill counts. This will include checks of protocol compliance and use of study drug in order to assess the reliability of subject-generated data. Subjects who fail to comply with the study requirements may be withdrawn from the study, following consultation with the sponsor.

The Investigator and clinical staff will make all efforts to ensure all enrolled subjects attend all study visits. If a subject missed a visit all efforts will be made to reschedule the visit within the time frame allowed in this protocol, which is 28±2 days from the previous visit. In case the subject cannot complete the visit in the appropriate time, the subject will continue to the next routine visit. If safety issues arise, an unscheduled visit may be done.

The Investigator and clinical staff will make all efforts to ensure all subjects' efficacy and safety scales are fully completed at each visit. If it is discovered that data is missing from these scales after they were initially completed, the Investigator or a member of the clinical staff can contact the subject, up until the following routine visit, to obtain this missing data. If missing data is not collected by the time of the following routine subject visit, no additional follow-up will be permitted, and this data will be considered missing. Details regarding the collection of this missing data (including time, date, data points collected and who collected them) will be documented in the source documents and the eCRF.

8.6 Screening Evaluations

The following scales or tests will be used for screening evaluations:

- UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria – (Appendix XI) will be used to confirm the Parkinson's disease diagnosis.
- Modified Hoehn & Yahr Stage (Appendix XII) The scale should be completed with the Investigator rating PD symptoms to confirm that the subject meets inclusion criteria related to stage of disease.
- Mini-Mental State Examination (MMSE) (Appendix XIII) MMSE, a 30 points questionnaire, will be completed to evaluate the subject for cognitive abilities necessary for study participation.
- Columbia Suicide Severity Rating Scale - baseline, CSSRS-BL, (Appendix VIII)
- UPDRS part III (Appendix IX)

9 STUDY CONDUCT

9.1 Study Period

The study duration per subject is 14 weeks in addition to up to 28 days for screening. The whole study duration is expected to be approximately 18-24 months.

9.2 Study Procedures

9.2.1 Detailed Study Plan

A detailed Schedule of Activities is provided in Appendix I.
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).

9.2.2 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 (see 16.4.2). 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.

9.2.3 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.

9.2.4 Visit 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

9.2.5 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.

9.2.6 Visit 4

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.

9.2.7 Visit 5

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.

9.2.8 Visit 6 – Treatment Termination

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

9.2.9 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

9.2.10 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.

9.2.11 Early Treatment/Study Termination Visit

Subjects who terminate treatment/study early (following first dose and prior to visit 6) according to criteria in section 7.5 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 schedule activities as in section 9.2.11.1. If a subject refuses 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.

9.2.11.1 Follow-up visits of subjects that have terminated the study treatment early

ETT subjects 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.**

10 CONCOMITANT MEDICATIONS

All concomitant medication that the subject is taking from the screening visit should be recorded on the concomitant medications log. In addition, any changes in concomitant medication or new medications added, including as a result of an inter-current illness must be recorded in the case report forms. A separate log will record anti-PD medications taken prior to enrollment.

10.1 Prohibited Medication

Subjects must not receive concomitant therapy with any of the following:

- 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.
- Non selective 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.

Care should be taken to avoid or minimize use of sympathomimetic medications, including nasal, oral and ophthalmic decongestants and cold remedies due to possible hypertensive reactions.
Care should be taken when giving study drugs with sedating medications (e.g. Diphenhydramine, Doxylamine Succinate and other first generation antihistamines) due to possible additive sedative effects with pramipexole.

Special attention should be given to symptoms and signs of serotonin syndrome, when an antidepressant is administered concomitantly with the study medication. Subjects who are taking

tricyclic or tetracyclic antidepressants, SSRIs, SNRIs or triazolopyridine antidepressants will be closely followed up by the PI for signs of serotonin syndrome, including:
agitation or restlessness, confusion, rapid heart rate and high blood pressure, dilated pupils, loss of muscle coordination or twitching muscles, muscle rigidity, heavy sweating, diarrhea, headache, shivering or goose bumps. At each periodic meeting, the DSMB will review adverse events and vital signs reported for subjects taking antidepressants concomitantly. Severe or serious adverse events for such subjects will be reported to the DSMB within 48 hours of receipt of the report by the sponsor.

10.2 Dietary Restrictions

Alcohol may increase symptoms of drowsiness or sudden onset of sleep that can be caused by pramipexole. Subject will be requested to limit alcoholic consumption to one glass of wine or one shot a day, and not within three hours before or after taking the study medication.
Dietary tyramine restriction is not ordinarily required with recommended doses of rasagiline. However, certain foods (e.g. aged cheeses, such as stilton cheese) may contain very high amounts (i.e. 150 mg) of tyramine and could potentially cause a hypertensive "cheese" reaction in subjects taking rasagiline, even at recommended doses, due to mild increased sensitivity to tyramine.

10.3 Rescue Therapy

No rescue therapy will be allowed during the treatment phase and the two weeks afterwards up until the safety follow up visit. If needed by the subject for adequate treatment of subject’s Parkinson's symptoms and according to the Investigator’s judgment the study medication will be discontinued and a rescue medication may be administered. This will be recorded on the concomitant medications log and in the reasons for treatment termination. Subject, who stopped taking study treatment prior to Visit 6, should return to the site for an Early Treatment Termination (ETT) visit as soon as possible. ETT subjects will be requested to continue with study visits and activities as planned, for follow up, without taking any study medication.

11 LABORATORIES

11.1 Safety Laboratory Tests

The safety laboratory tests (chemistry, hematology, coagulation and urinalysis see Appendix II), 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,
Bergschot 71, 4817 PA Breda, Netherlands for sites in Europe and Eurofins Central Laboratory US 2430 New Holland Pike, Lancaster, PA 17601 for sites in USA and Canada.

The tests will be done according to Eurofins Central Laboratory written Standard Operating Procedures. Any value outside the normal range will be flagged for the attention of the Investigator or designee at the site. The Investigator or designee will indicate whether or not the value is of clinical significance.

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.)

The central laboratory will perform all clinical laboratory tests. Detailed shipping/handling instructions of laboratory supply will be provided in a separate laboratory manual.

11.2 Vital Signs, Height and Weight

Respiration rate (RR per minute) and temperature will be measured, with the subject in the seated position for at least 5 minutes, at the visits specified in the Schedule of Activities. Orthostatic measurements (lying and standing BP and 30 seconds of radial pulse) can be measured manually or using an automated BP machine and will be measured at every clinic visit, except visit 3 that is done for titration evaluation of Pramipexole ER or matching placebo. The subject's BP and HR will be measured after the subject has been lying for approximately 5 minutes. The subject will be instructed to rise to a standing position, and a BP measurement will be taken after the subject has been standing for 3 minutes. HR will be determined for a period of 30 seconds.

All BP and HR measurements will be taken using the writing arm of each subject.

Additional vital signs will be obtained at the discretion of the Investigator if clinically significant signs or symptoms occur.

The subject's weight will be measured at every clinic visit except visit 3 that is done for titration evaluation of Pramipexole ER or matching placebo. The subject's height will only be measured at the Screening visit.

11.3 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 initialed and dated by the Investigator.

12 STUDY DRUGS SUPPLY

12.1 Drug Manufacturing

Capsules of P2B001, its individual components (pramipexole and rasagiline) and matching placebo were manufactured by Catalent Pharma solutions Somerset, USA, address: Schoolhouse Rd. 14 Somerset, NJ 08873, USA.
Pramipexole ER tablets and matching placebo were purchased from Dr. Reddy's Laboratories Limited, FTO UNIT 3, Survey No 41 Bachupally village Qutubullapur Mandal
Ranga Reddy District Telangana 500090 India

All bottle closures are tamper proof and child resistant.

12.2 Treatment Assignment and Randomization

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 subject. 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.

12.3 Packaging and Labeling

The study medication will be packed and labeled by Almac Group limited, 25 Fretz Road, Souderton, PA 18964, USA.
The study kit will include an outer box containing 4 inner boxes;

- Weeks 1-4 box containing three bottles: one bottle of capsules of either P2B001/RAS 0.75/PPX 0.6/placebo once daily (33 capsules) (bottle C, labeled with a blue stripe), one bottle with tablets of either Pramipexole ER 0.375 mg or matching placebo (30 tablets), (bottle A, labeled with a yellow stripe) and one bottle with either Pramipexole ER 1.5 mg or matching placebo (30 tablets), (bottle B, labeled with a pink stripe).
- Two identical boxes for weeks 5-12. Each box containing 4 bottles: one bottle of capsules of either P2B001/RAS 0.75/PPX 0.6/Placebo (33 capsules) and 3 identical bottles with Pramipexole ER 1.5 mg or matching placebo tablets (30 tablets each).
- Week 13 One box containing two bottles: one bottle of tablets of either Pramipexole ER 0.375 mg or matching placebo (30 tablets) and one bottle of tablets of either Pramipexole ER 1.5 mg or matching placebo

For subject's convenience the bottles are labeled with different colored stripes. The bottle of P2B001/RAS 0.6/PPX 0.75/placebo is labeled with a blue stripe named bottle C. The bottle of Pramipexole ER 0.375 mg/matching placebo is labeled with a yellow stripe named bottle A and the bottle of Pramipexole ER 1.5 mg/matching placebo is labeled with a pink stripe named bottle B.
The whole study kit with the 4 inner boxes will be dispensed to the subject on visit 2. No further dispensing is needed on other visits. The subject will be requested to bring the used inner box with him/her for the next visit as follows:

- Visit 4: return of box weeks 1-4.
- Visit 5: return of box used during weeks 5-8 (1 out of 2 Week 5-12).
- Visit 6: return of box used during weeks 8-12 (2 out of 2 Week 5-12).
- Visit 7: return of box week 13

Since this product is intended for once daily dosing, there is no need for the subject to carry the medication with him/her throughout the day, therefore, the subject will be instructed to keep the

bottles with the kit box throughout the study. The outer box and each inner box will tamper evident sealed.

The master English version of the labels on the bottles will include at least the following information as follows:

Label for P2B001 /RAS 0.75mg / PPX 0.6mg / placebo bottle:

- Study number: P2B001/003
- Kit number
- Subject number
- Subject initials
- Site number
- Contents: 33 capsules, containing: Pramipexole / Rasagiline once daily 0.6/0.75 mg or Pramipexole 0.6 mg or Rasagiline 0.75 mg or placebo (Exp: mm/yyyy)
- Storage conditions: 59°F - 77°F (15°C - 25°C).
- Protect from exposure to high humidity.
- Take 1 capsule by mouth with a glass of water (8oz or 240ml), do not chew, crush or cut. For further dosing instructions see "dosing instruction leaflet" provided by the clinical staff.
- Packaging batch number
- Caution: new Drug Limited by Federal (or United States) law to Investigational use / for clinical trial use only/ Investigational drug. To be used by qualified investigators only.
- Keep out of the reach of children.
- Do not remove or ingest moisture resistant bags or canisters from the bottle.
- Return all empty, partially used or unused bottles from the current box to the clinic for accountability.
- Sponsor name and location

Label for Pramipexole ER tablets 1.5 mg / matching placebo bottle:

- Study number: P2B001/003
- Kit number
- Subject number
- Subject initials
- Site number
- Bottle # ____ out of _____
- Contents: 1 x 30 tablets, containing Pramipexole 1.5 mg or placebo (exp: mm/yyyy)
- Storage conditions: 59°F - 77°F (15°C - 25°C).

- Take caplet/s by mouth with a glass of water (8oz or 240ml), do not chew, crush or cut. For further dosing instructions see “dosing instruction leaflet” provided by the clinical staff.
- Packaging batch number
- Caution: new Drug Limited by Federal (or United States) law to Investigational use / for clinical trial use only/Investigational drug. To be used by qualified investigators only.
- Keep out of the reach of children.
- Do not remove or ingest moisture resistant bags or canisters from the bottle.
- Return all empty, partially used or unused packages from the current box to the clinic for accountability.
- Sponsor name and location
- Protect from exposure to high humidity.
- Please keep the bottles with the kit box together at all times.

Label for Pramipexole ER tablets 0.375 mg / matching placebo bottle:

- Study number: P2B001/003
- Kit number
- Subject number
- Subject initials
- Site number
- Contents: 1 x 30 tablets, containing Pramipexole 0.375 mg or placebo (exp: mm/yyyy)
- Storage conditions: 59ºF - 77ºF (15ºC - 25ºC).
- Take tablet/s by mouth with a glass of water (8oz or 240ml), do not chew, crush or cut. For further dosing instructions see “dosing instruction leaflet” provided by the clinical staff.
- Packaging batch number
- Caution: new Drug Limited by Federal (or United States) law to Investigational use / for clinical trial use only/Investigational drug. To be used by qualified investigators only.
- Keep out of the reach of children.
- Do not remove or ingest moisture resistant bags or canisters from the bottle.
- Return all empty, partially used or unused packages from the current box to the clinic for accountability.
- Sponsor name and location
- Protect from exposure to high humidity
- Please keep the bottles with the kit box together at all times.

The following information will be included on the Inner boxes label (up titration box, maintenance box and down titration box):

- Study number: P2B001/003
- Box type (either weeks 1-4, Weeks 5-12, Weeks 13)
- Kit number
- Subject number
- Subject initials
- Investigator name
- Site number
- Contents (one or more of the following, as relevant):
    - 33 capsules, containing: Pramipexole / Rasagiline once daily 0.6/0.75 mg or Pramipexole 0.6 mg or Rasagiline 0.75 mg or placebo. (Exp: mm/yyyy)
    - 30 tablets, containing Pramipexole 1.5 mg or placebo (Exp: mm/yyyy)
    - 30 tablets, containing Pramipexole 0.375 mg or placebo (Exp: mm/yyyy)
- Storage conditions: 59°F - 77°F (15°C - 25°C). Take by mouth with a glass of water (8oz or 240ml), do not chew, crush or cut. For further dosing instructions see "dosing instruction leaflet" provided by the clinical staff.
- Packaging batch number
- Caution: new Drug Limited by Federal (or United States) law to Investigational use / for clinical trial use only/Investigational drug. To be used by qualified investigators only.
- Keep out of the reach of children.
- Return all empty, partially used or unused packages from the current box to the clinic for accountability.
- Sponsor name and location
- Protect from exposure to high humidity
- Please keep the bottles with the kit box together at all times.

The following information will be included in the Outer box label:

- Study number: P2B001/003
- Kit number
- Earliest expiry date
- Subject number
- Subject initials
- Investigator name
- Site number

- Kit content
- Storage conditions: 59ºF - 77ºF (15ºC - 25ºC).
- Packaging batch number
- Caution: new Drug Limited by Federal (or United States) law to Investigational use / for clinical trial use only/Investigational drug. To be used by qualified investigators only.
- Keep out of the reach of children.
- Sponsor name and location
- Protect from exposure to high humidity
- Take by mouth with a glass of water (8oz or 240ml), do not chew, crush or cut.
- For further dosing instructions see "dosing instruction leaflet" provided by the clinical staff.

Specific information or language required for sites in Canada and Europe will be included according to local regulations of each country. The kit label to Canadian sites will include at least a French translation. The kit label to the European sites will include the relevant translation per the main language of the European country

12.4 Distribution and Shipment

Study drugs will be shipped to the study site, under the sponsor's responsibility.
The study drugs will be shipped and stored in room temperature between 15° and 25°C (59°F-77°F). Protect from exposure to high humidity and light.
All study drugs and materials will be packed in appropriate storage boxes.
If, upon arrival at the investigational site, the study drugs appear to be damaged, the sponsor should be contacted immediately.
Each shipment of study drugs for the study will contain a shipment form describing the content of shipment. This form will assist in maintaining current and accurate inventory records. When a shipment is received, the site Investigator/coordinator/pharmacist or depot will acknowledge receipt of the study drugs by signing the relevant shipping documents.

12.5 Storage, Dispensing and Return

The study drugs will be kept in a secure, limited-access, controlled storage area.
Only authorized personnel will have access to the study drugs. The study site personnel at each site will be responsible for correct storage and handling of the study drugs. Drug storage temperature will be monitored and recorded on a daily basis.
The study drugs will be dispensed by the study site pharmacist or by other authorized personnel.
All unused capsules/tablets and all full, empty or partially empty bottles will be returned to the sponsor by the site monitor after a full reconciliation of the site's study drug inventory against the site's drug accountability records has been performed.

The retest dates will be managed by the Randomization Trial Supply Management (RTSM) system.

12.6 Verification of Compliance with Treatment Regimen

Subjects will be instructed to bring the last medication box used (open and unopened bottles) with them to visits 4, 5, 6 and 7 for compliance and accountability checks. During each study visits, (visits 4-7), the Investigator and/or site coordinator will assess the subject's compliance with the prescribed regimen for the study medication. This will include checks of protocol compliance and use of study drug in order to assess the reliability of subject-generated data. Subjects who fail to comply with the study requirements may be withdrawn from the study, following consultation with the sponsor.

Compliance with the dosing regimen will be determined by performing study drug accountability of returned study drugs used and unused. The number of used, unused and lost capsules will be recorded in the study drug accountability records and the eCRF by site personnel at every post randomization visit.

A subject will be considered non-compliant if he/she misses more than 4 doses of study medication within a 28 day period (less than 85% compliance). Examples of reasons for missing a dose are 1) if a subject develops an adverse event that the Investigator believes requires the subject's dose to be held, or 2) if a subject loses their kit of study medication and a replacement kit is requested, which should arrive at the site within 1-2 days (3-4 days if a weekend is involved).

12.7 Accountability

For study drug accountability, the subject will be requested to bring for visits 4-7, all empty, partially used or unused bottles from the box used during the previous month. During these visits (visits 4, 5, 6/ETT and 7) the site staff will count the remaining capsules and tablets that the subject brought with him and document the results in accountability records. Only the opened box that was used during the last visit will be brought for the accountability. Accountability of the entire study medications kit (with all boxes and bottles left) will be done at ETT visit for ETT subjects.

The Investigator is responsible for the control of study drugs under investigation. Adequate records of the receipt and disposition of the study drug must be maintained.

Study drugs accountability records should contain the following information:

- Shipment number, kit numbers, batch number, number of kits and date received for all shipments of study drug received by the site
- Subject number, medication kit number, the date, batch number, and quantity of study drug dispensed to AND returned by the subject (when applicable)

- Kits numbers, batch number, number of kits (un-dispensed study drug) or number of capsules/tablets (returned study drug) for all study drug returned to the Sponsor

During each site visit, the monitor will review all study drugs accountability records and study drug inventory on-site.

12.8 Study End

Once the study site has been closed out by the monitor all remaining unused and partially used drug supplies must be returned to the sponsor. Once this has been done, the corresponding accountability records must be kept at the study sites and a photocopy of these records will be sent to the sponsor.

12.9 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 will all be blinded to the subject assignment. Specific, independent, unblinded study personnel from the CRO will be available to provide the DSMB with periodic reports.

12.9.1 Emergency Code Breaking

Emergency code breaking will be managed by the IWR/IVR system. The randomization code may be broken by the Investigator when urgent action is required for the clinical management of the patient. Typically, code breaks will occur only in emergency situations which may include the management of a serious adverse event. If possible, the sponsor, or designee, should be contacted to discuss the case before the code is broken.
If it becomes necessary to break the code during the study, the name of the person who breaks the code, the date, time and reason will be recorded in the RTSM. The reason for the break of the code should also be documented in the eCRF. The Investigator should promptly document and explain to the Sponsor, or designee, any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product.

13 SAFETY/ADVERSE EVENTS

13.1 Adverse Events definition

An adverse event is any untoward medical occurrence in a clinical investigation subject who is administered a medicinal product whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease (new or exacerbated), temporally associated with the

use of a medicinal product, whether or not considered related to the product. Pre-existing signs and symptoms should not be considered AEs unless they worsen unexpectedly post-study drug administration. In addition, any study procedure-related AE that occurs after study participants have signed the Informed Consent Form (ICF) and prior to administration of the first dose of study drug will be recorded as an AE. Any adverse event that occurs post-study drug administration will be considered a treatment-emergent AE. Any adverse event that occurs prior-study drug administration will be considered a baseline-emergent AE. Again, all events should be entered whether or not the event is considered to be related to the study drug.

The date of onset, a description of the AE, severity, seriousness, action taken, relationship to the study drugs (causality), outcome of the event and date of resolution will be recorded. The final study report will include all of these details for each AE as well as the calculated duration.

The Investigator will assess the severity of the AE as:

- mild: AE which is easily tolerated
- moderate: AE sufficiently discomforting to interfere with daily activity.
- severe: AE which prevents normal daily activities.

The Investigator will assess the causality of the AE as (see section 13.2):

- unrelated
- possibly related
- probably related

13.2 AE Causality Definitions

TERM	DEFINITION	CLARIFICATION
Unrelated	This category applies to those AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.)	
Possibly	This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty.	An AE may be considered possibly related if or when (at least two of the following): • It follows a reasonable temporal sequence from administration of the drug. • A causal relationship to the experimental treatment cannot be reasonably excluded and an alternative explanation (e.g., concomitant medication or concomitant disease) cannot be excluded or reasonably suggested as causing the AE. • It follows a known pattern of response to the test drug.
Probably	This category applies to those AEs which, after careful medical consideration at the time	An AE may be considered probably related if or when (at least three of the following):

TERM	DEFINITION	CLARIFICATION
	they are evaluated, are felt with a high degree of certainty to be related to the test drug.	• It follows a reasonable temporal sequence from administration of the drug. • It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • It follows a known pattern of response to the test drug.

In case of an AE, the Investigator will initiate appropriate treatment according to his medical judgment and will decide whether to withdraw the subject from the study. Subjects should be followed clinically until all parameters (including laboratory tests) have either returned to normal, or are otherwise explained.

An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it:

- results in subject's withdrawal by the Investigator
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- is considered by the physician to be of clinical significance

All adverse events will be recorded in the source documents for all study subjects from the signing of the ICF until the subject has completed the study (i.e., following completion of Visit 7 (week 14) or screen fails or prematurely discontinues from the study, whichever occurs first. For randomized subjects all adverse events will be recorded in the eCRF. For screen failure subjects, adverse events will be captured only in the source documents and not in the eCRF.

13.3 Reporting Orthostatic Hypotension as AE

Only the following instances of orthostatic hypotension need to be recorded as an adverse event:

- Any drop in systolic or diastolic blood pressure that the PI deems is clinically significant. The decision could be based on observations during the visit or if a subject complains of symptoms related to orthostatic hypotension, however, this is left ultimately to the judgment of the PI.
- A drop of over 30 mm Hg in systolic or 20 mm Hg in diastolic blood pressure should automatically be considered as clinically significant, even if asymptomatic, and thus should be captured as an adverse event.

13.4 Serious Adverse Event (SAE)

An SAE is defined as an AE that results in any of the following outcomes:

- death
- life-threatening
- requires inpatient hospitalization or prolongs hospitalization
- persistent or significant disability/incapacity
- a congenital abnormality or birth defect
- an important medical event which requires medical intervention to prevent the above outcomes.

Important medical events are those which may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; resulting in an adverse event will normally be considered serious by this criterion.

13.5 SAE Reporting

Any AE meeting the definition of serious, occurring after signing of informed consent or during 30 days after the last dose administration and, from then on, only if the study treatment is assessed as "suspected" with regard to causality, must be recorded on the SAE Report Form provided by PRA Health Science. The SAE must be reported within 24 hours from the Investigator's knowledge of its occurrence to:

Sites in Europe:
PRA Drug Safety Centre Email (EAPA): MHGSafety@prahs.com
PRA Drug Safety Centre Fax (EAPA): + 44 (0) 1792 525 720
PRA Safety Helpline EAPA: +49 621 8782 154
Sites in USA and Canada:
PRA Drug Safety Centre Email (NA): CHOSafety@prahs.com
PRA Drug Safety Centre Fax (NA): 1-888-772-6919
PRA Safety Helpline NA: 1-800-772-2215

The Investigator must be prepared to supply the sponsor with the following information:

a) Investigator name and center number
b) Subject ID number
c) Medication kit number
d) Subject initials
e) Subject demographics
f) Clinical Event
g) description

h) date of onset
i) severity
j) treatment (including hospitalization)
k) relationship to study drug (causality)
l) action taken regarding study drug
m) if the SAE was Fatal or Life-threatening
cause of death (whether or not the death was related to study drug)
autopsy findings (if available)
n) Medical History case report form (copy)
o) Concomitant Medication case report form (copy)
p) Any relevant laboratory reports

Follow-up information or new information about any SAE should be forwarded by the site to PRA Health Science Safety within 24 hours of the information becoming available. This information should be sent to the sponsor's appointed safety monitor.
The clinical site will be responsible for notifying their IRB and the subject's General Practitioner of all SAEs that occur at their site.
The sponsor/CRO will submit a summary of the clinical course of the SAEs to the authorities, according to regulations.
Subjects who have had an SAE must be followed clinically until all parameters (including laboratory) have either returned to normal, stabilized or are otherwise explained.

Overdose:
Taking more than 1 capsule per day and/or more than 4.5 mg of pramipexole ER or matching placebo is considered an overdose. Cases of overdose, whether accidental or intentional, that result in serious adverse reactions are to be reported as an SAE within one business day after the Investigator becoming aware of the overdose. The overdose should be reported on the standard SAE report form and sent to PRA Safety using the information below.
Sites in Europe:
PRA Drug Safety Centre Email (EAPA): MHGSafety@prahs.com
PRA Drug Safety Centre Fax (EAPA): + 44 (0) 1792 525 720
PRA Safety Helpline EAPA: +49 621 8782 154
Sites in USA and Canada:
PRA Drug Safety Centre Email (NA): CHOSafety@prahs.com
PRA Drug Safety Centre Fax (NA): 1-888-772-6919
PRA Safety Helpline NA: 1-800-772-2215

All cases of overdoses, even if not associated with adverse reactions, shall be recorded within EDC, including symptoms, corrective treatment and outcome of overdose.

13.6 Pregnancy

Should a pregnancy occur, it must be reported and recorded on a pregnancy report form. However, pregnancy is not regarded as an AE for the purposes of this protocol, unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (i.e., spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are to be considered SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications will not be regarded as AEs.

13.7 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Adverse reactions are all untoward and unintended responses to the investigational product related to any dose administrated. Unexpected adverse reaction is those of which the nature, or severity, is not consistent with the applicable product information.

All SUSARs should be reported to the authorities.

Investigators will also be notified of all unexpected, serious, drug-related events (i.e., 7- or 15-day expedited safety reports) that occur during the clinical trial; those events will be reported to the site in a blinded fashion. Each site is responsible for notifying its IRB of these expedited safety reports, in accordance with applicable site practices.

14 DATA MANAGEMENT AND QUALITY ASSURANCE

14.1 Handling of Data

An Electronic Data Capture (EDC) system to collect subject electronic Case Report Form (eCRF) information will be used. All the information collected during the study will be recorded in the eCRF identified by subject initials and subject ID number, for each subject enrolled, including those removed for any reason after administered the first dose. It is the responsibility of the Investigator and Co-Investigator to ensure that the eCRFs are properly and completely filled in.

Central data management will be performed by PRA. Internet-based remote data capture will be used for entering, managing, and validating data from centers. The following regulation will be followed:

- FDA 21CRF part 11 rule
- ICH, Good Clinical Practice, Consolidated guideline
- FDA Guidance for Industry “Computerized system used in clinical trials.
- EU Directives

14.2 Coding of Adverse Events, Drugs and Diseases

All AEs will be coded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA) latest version. Concomitant medications will be coded according to the WHO drug dictionary.

14.3 Data Quality Assurance

All aspects of the study will be carefully monitored with respect to Good Clinical Practices (GCP) and SOPs for compliance with applicable government regulations. The study monitor will be an authorized individual designated by the Sponsor. The study monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the PI. Study monitoring will be conducted according to a monitoring plan.

15 STATISTICAL METHODOLOGY

This study is a phase 3, twelve-week, multi-center, multinational, randomized, double-blind, double-dummy, parallel group study. Up to 525 eligible subjects with early untreated Parkinson's disease (PD) who are not early terminated from the study during screening or baseline visits and are randomized to treatment with P2B001 0.6/0.75 (150 subjects), or pramipexole 0.6 mg once daily (150 subjects), or rasagiline 0.75 mg once daily (150 subjects), or pramipexole ER titrated to therapeutic optimal dose (75 subjects) 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 PI and the central EMC.

This study is powered to demonstrate the superiority of (i) P2B001 0.6/0.75mg as compared to its individual components in the change from baseline to Week 12/Treatment Termination in Total UPDRS score and, (ii) to demonstrate the superiority of P2B001 0.6/0.75mg over pramipexole ER in the change from baseline to Week 12/Treatment Termination in the ESS.

Treatment with pramipexole ER will serve as a calibration arm to better characterize P2B001 against currently used therapy. Therefore, with the exception of change from baseline to Week 12/Treatment Termination in the ESS, only descriptive statistics and no formal significance testing will be made between the pramipexole ER arm and the other three study arms.

Week 12/Treatment Termination is defined for all statistical analyses involving significance testing as the last visit in which a subject was treated with the study drug.

15.1 Sample Size Rationale

The study was powered to allow achieving two goals:

- 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 arm 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.

- 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 arm, 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%.

15.2 Sample Size Re-Assessment

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 protocol amendment.

15.3 Randomization

Randomization will take place following the completion of all screening procedures including subject approval by both site PI and the central EMC.
Up to 525 eligible subjects with early untreated Parkinson's disease (PD) who are not early terminated from the study during screening or baseline visits and are 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.

15.4 Data Analyses Sets

The following data analysis sets are defined for this study:

- **Intention-to-Treat Analysis Set (ITT)**: The ITT Analysis Set will include all eligible and randomized subjects who are not early terminated from the study during screening or baseline visits according to the treatment group to which they are originally randomized to. The Intention-to-Treat (ITT) analysis set will serve as the principal analysis set for efficacy assessments
- **Modified Intention-to-Treat Analysis Set (mITT)**: The mITT Analyses Set is a subset of the ITT Analysis Set including subjects who have at least one post-baseline UPDRS assessment and have taken at least one study drug dose according to the treatment group to which they are originally randomized to.
- **Completers Analysis Set (CO):** The completers analysis set (CO) will consist of all subjects who complete the 12 weeks of the study according to treatment actually administered.
- **Per Protocol Analysis Set (PP):** The per-protocol analysis set (PP) will consist of all subjects included in the CO analysis set without any major protocol violations according to treatment actually administered.
- **Safety Analysis Set (ST):** The safety analysis set (ST) will consist of all subjects who have been randomized and received at least one study drug according to treatment actually administered. The safety analysis set (ST) will serve as the principal analysis set for safety assessments.

15.5 Overall Significance Level and Multiplicity Adjustment:

The overall significance level for this study will be 5% using two-tailed tests. No interim analyses or futility analyses are planned for this study.

The overall, experiment-wise type-I error rate of 5% will be preserved according to the below plan:

1. The principal analysis of the primary endpoint is designed to demonstrate the efficacy of P2B001 0.6/0.75mg as compared to its individual components in the changes from baseline to Week 12/Treatment Termination. Accordingly, analysis will employ two contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily. The type-I error of 5% for multiple contrasts testing for the primary endpoint will be preserved by determining that the primary endpoint is met only if both comparisons will favor P2B001 0.6/0.75mg at a two-tailed alpha level of 5% each.
2. Multiplicity adjustment for multiple endpoints testing for the secondary endpoints will utilize the gate keeping hierarchical method according to the following order and plan:
   - For the 1st secondary endpoint, namely, the P2B001 0.6/0.75mg vs. Pramipexole ER contrast in the change from baseline to Week 12/Treatment Termination in the ESS, will be considered as met only if both primary endpoint contrasts as above defined and the P2B0011 0.6/0.75mg vs. pramipexole ER contrast in the change from baseline to Week 12/Treatment Termination in the ESS will all be met (total of 3 contrasts) at a two-tailed alpha level of 5% each.
   - The 2nd secondary endpoint, namely, the change from baseline to Week 12/Treatment Termination visit in the Total PDQ39 will be considered as met if all of the 3 previous tested contrasts (primary endpoint and 1st secondary endpoint) as well the two contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 2nd secondary endpoint will all be met (total of 5 contrasts) at a two-tailed alpha level of 5% each.
   - The 3rd secondary endpoint, namely, the change from baseline to Week 12/Treatment Termination visit in the ADL UPDRS (part II) score will be considered as met if all of the 5 previous tested contrasts (primary endpoint, 1st and 2nd secondary endpoints) as well the two contrasts: P2B001 0.6/0.75mg vs. Pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 3rd secondary endpoint will all be met (total of 7 contrasts) at a two-tailed alpha level of 5% each.
   - The 4th secondary endpoint, namely, the change from baseline to Week 12/Treatment Termination visit in the motor UPDRS (part III) score will be considered as met if all of the 7 previous tested contrasts (primary endpoint, 1st, 2nd and 3rd secondary endpoints) as well the two contrasts: P2B001 0.6/0.75mg vs. Pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 4th secondary endpoint will all be met (total of 9 contrasts) at a two-tailed alpha level of 5% each.

- The 5th secondary endpoint, namely, the CGI-S responder's analysis at Week 12/Treatment Termination visit (change from baseline ≥1 CGI-S points) will be considered as met if all of the 9 previous tested contrasts (primary endpoint, 1st, 2nd, 3rd and 4th secondary endpoints) as well the two contrasts: P2B001 0.6/0.75mg vs. Pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 4th secondary endpoint will all be met (total of 11 contrasts) at a two-tailed alpha level of 5% each.

15.6 Study Population Summary

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

15.6.1 Subject Disposition

Data from subjects who are randomized, subjects who are randomized regardless of treatment (ITT), mITT, CO, PP and ST analysis sets, subjects who have reached the End of Study visit according to study plan, subjects who early discontinued treatment or study follow-up will be summarized. Data from subjects who early discontinued study IP treatment or study follow-up will also be displayed by discontinuation reason using descriptive statistics. The denominator for calculating the percentages will be the set of ITT. This summary table will also describe all subjects screened into the study.

15.6.2 Study Inclusion and Exclusion Criteria

Although it is expected that all subjects randomized into the study will meet all study inclusion and exclusion criteria there might be some subjects that will be granted waivers allowing them to be enrolled into the study. The number and proportion (%) of the ITT analysis set subjects who failed to meet study inclusions/exclusion criteria will be reported broken down by criteria.

15.6.3 Demographics and Baseline Characteristics

Demographics and baseline data will be displayed for the ITT analysis set. Subject demographic and baseline characteristics, including baseline prognostic factors will be examined to assess the comparability of the treatment groups. For continuous variables, descriptive statistics (number [n], mean, standard deviation (SD), 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.

Summary statistics of these parameters will also be provided when broken down by geographical region, and by US/Non-US sub-populations.

15.6.4 Medical History

The incidence (no. of patients) of past medical conditions will be provided when broken down by System Organ Class (SOC) and Preferred Term (PT) according to MedDRA dictionary. Subjects

with at least 1 past medical condition in each SOC/PT category will be summarized using descriptive statistics. Subjects will be counted only once in each category.

15.6.5 Prior and Concomitant Medications

All prior and concomitant medications will be coded using the WHODRUG dictionary. The incidence of prior medications and separately those consumed concomitantly; from the day of 1st study IP administration and onwards, will be summarized using descriptive statistics by Therapeutic Main Group (ATC Level 2) and dictionary Preferred Term.
Subjects will only be counted once in each Therapeutic Main Group, and only once in each Preferred Term category.

15.6.5.1 Pre-Study Medications

Analyses will include only coded medications that were initiated one day or more prior to the 1st administration of study IP. Medications in which start date will not be reported in the database will also be considered as pre-study medications.
Incidence table including subject counts (no. of subjects) and percentages broken down by Therapeutic Main Group and Preferred Term as well as by treatment group will be generated.
Summary statistics of pre-study medications will also be provided when broken down by US/Non-US sub-populations.

15.6.5.2 Concomitant Medications

Analyses will include only coded medications that were consumed after 1st study IP administration. Medications in which start date will not be reported in database will also be considered as concomitant medications. Medications lacking stop date will be considered as ongoing for the purpose of analysis.
Incidence table including subject counts (no. of subjects) and percentages broken down by Therapeutic Main Group and Preferred Term as well as by treatment group will be generated.
Summary statistics of concomitant medications will also be provided when broken down by US/Non-US sub-populations.

15.6.5.3 Disallowed Medications Use

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.

Incidence table including subject counts (no. of subjects) and percentages broken down by treatment group will be generated and data listing will be provided.

15.6.6 Protocol Violations/Deviations

Protocol deviations and violations will be recorded on an ongoing basis and will be included in a DV domain in the SDTM database.

The number of subjects with at least 1 protocol violation/deviation in each category will be summarized using descriptive statistics. Detailed individual subject listing will also be provided.

15.6.7 Efficacy Endpoints and Analyses

All efficacy endpoints will be tested for the ITT analysis set controlling for multiplicity as detailed in Section 15.5.

An effort to obtain the efficacy outcome measures data regardless if study treatment was discontinued will be made.

Week 12/Treatment Termination is defined for all statistical analyses involving significance testing as the last visit in which a subject was treated with the study drug.

15.6.8 Primary Efficacy Endpoint and Principal Statistical Analysis

The primary efficacy endpoint for this study is the change from baseline to Week 12/Treatment Termination in total UPDRS score (defined as sum of parts II and III, scores (0-160). The statistical

model will be a Mixed Model for Repeated Measures (MMRM) (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical week in trial by treatment interaction, country or geographical region (CGR), and baseline 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 changes form baseline to post-baseline visits (weeks 4, 8 and 12) collected from all subjects randomized into the study will be used as response in the model. The differences between the P2B001 0.6/0.75mg arm as compared to its 2 individual components at Week 12/Treatment Termination will be estimated and tested using 2 contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg and P2B001 0.6/0.75mg vs. rasagiline 0.75mg. The study primary endpoint will be considered as met only if both contrasts will favor P2B001 0.6/0.75mg at a two-tailed alpha level of 5% each.

15.6.9 Sensitivity Analyses for the Primary Endpoint

The robustness of the results of the principal analysis of the primary endpoint will be explored employing the following:

15.6.9.1 Sensitivity Analysis Using Difference Analyses Sets

The primary analysis described above will be used for the ITT, mITT, CO and PP Analysis Sets with or without efficacy measurements taken after study treatment termination.

15.6.9.2 Sensitivity Analysis Using Change from Baseline to Last Observed Value (LOV)

The Total UPDRS score change from baseline to last observed value (LOV), with or without UPDRS measurements taken after study treatment termination, will be calculated and analyzed for the ITT Analysis Set.

The statistical model to be used for the analysis of the change from baseline to LOV in the Total UPDRS score will be an analysis of covariance (SAS® MIXED procedure) and the model will include treatment group, CGR and baseline Total UPDRS score. The change from baseline to LOV will be used as response variable in the model and differences between P2B001 0.6/0.75mg to its 2 individual components at LOV will be tested using 2 contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg and P2B001 0.6/0.75mg vs. rasagiline 0.75mg.

15.6.9.3 Sensitivity Analysis Using the Total UPDRS Responders Analysis

The ITT analysis set will further be used to compare the LOV responders' rate, with or without UPDRS measurements taken after study treatment termination, between the P2B001 0.6/0.75mg and its 2 individual components in the primary endpoint.

A subject with an improvement of 4 point or more at LOVas compared to baseline will be classified as a "Responder" while other randomized subjects not falling into this definition will be classified as a "Non-Responders".

The analysis of this binary end-point will be based on estimating 2 contrasts (2 contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg and P2B001 0.6/0.75mg vs. rasagiline 0.75mg) derived from a baseline-adjusted, Logistic Regression model [SAS® PROC GENMOD with DIST=BIN and LINK=LOGIT] to this binary outcome measure. In addition to the treatment group the model will include the following covariates: CGR and baseline Total UPDRS score. The treatment effect (odds-ratios) of P2B001 0.6/0.75mg vs its 2 individual components at LOV on the proportion of responders at week 12/Treatment Termination and the corresponding adjusted proportions will be displayed. In addition, the number and proportion of responders at Week 12/Treatment Termination will be displayed by treatment group.

15.6.9.4 Sensitivity Analysis Accounting for Missing Values

The ITT analysis set will be used for the below sensitivity analysis.

To evaluate the possible impact of missing values on the principal analysis of the primary endpoint results assuming all missing data are Missing Not At Random (MNAR), a sensitivity analysis using the **Tipping Point Method** and multiple imputations will be performed according to the following steps:

1. Multiple Imputations Assuming Missing At Random Missingness Mechanism: The Multiple Imputations procedure, using the Markov-Chain-Monte-Carlo (MCMC) method (SAS® MI procedure) will be used on the total UPDRS at baseline and at LOV, with or without UPDRS measurements taken after study treatment termination, to impute Missing At Random (MAR) missing values. Treatment and country will be included in the imputation model.
   The number of imputations that will be used will be 100. Minimum and maximum imputation values will be 0 and 160 in line with the total UPDRS score range. The seed that will be used for the MI procedure random numbers generator will be 12345678.
2. The change from baseline based on step 1 will then be calculated.
3. For the P2B001 0.6/0.75mg -treated subjects only with imputed missing values, the value of **S**, the tipping parameter, where **S**$\geq$0 (reduction over time is an improvement), will be added to the calculated change from baseline artificially worsening the change for these imputed values.
4. Each of the 100 imputed data sets for a given **S** will be analyzed using an ANCOVA model (SAS® MIXED procedure) to derive the treatment effect of the P2B001 0.6/0.75mg vs its 2 individual components and standard errors. The model will include treatment, country and baseline Total UPDRS score.
5. Treatment effects, 95% CIs and p-values will be calculated for a given **S** using the SAS® MIANALYZE procedure on the treatment effects and SE estimates for each of the 100 imputed datasets.

6. Imputations and analyses will be repeated while increasing **S** by 1% each time until one of the two p-values (for the two between groups contrasts) in the primary model will be greater than 0.05. The first **S** causing significance on both contrasts to be lost is the **tipping point**.

15.6.10 Key Secondary Efficacy Endpoints and Analyses

All efficacy endpoints will be tested for the ITT analysis. Secondary endpoints will be tested once both primary endpoint contrasts (P2B001 0.6/0.75mg as compared to its individual components) will favor P2B001 0.6/0.75mg at a two-tailed alpha level of 5% each.
Multiplicity adjustment for multiple endpoints testing for the secondary endpoints will utilize the gate keeping hierarchical method according to the following order and plan:

15.6.10.1 Change from Baseline to Week 12/Treatment Termination in the ESS

For the 1st secondary endpoint, namely, the P2B001 0.6/0.75mg vs. Pramipexole ER contrast in the change from baseline to Week 12/Treatment Termination in the ESS, will be considered as met only if both primary endpoint contrasts as above defined and the P2B001 0.6/0.75mg vs. pramipexole ER contrast in the change from baseline to Week 12/Treatment Termination in the ESS will all be met (total of 3 contrasts) at a two-tailed alpha level of 5% each.
The statistical model to be used for the analysis of the change from baseline to Week 12/Treatment Termination in the ESS will be a Mixed Model for Repeated Measures (MMRM) (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical week in trial by treatment interaction, CGR, and baseline ESS 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 changes form baseline to post-baseline visits (weeks 5, 8 and 12) collected from all subjects randomized into the study will be used as response in the model. The difference between the P2B001 0.6/0.75mg as compared to Pramipexole ER at Week 12/Treatment Termination will be estimated and tested using a contrast.

15.6.10.2 Change from Baseline to Week 12/Treatment Termination in the Total PDQ39

The 2nd secondary endpoint, namely, the change from baseline to Week 12/Treatment Termination visit in the Total PDQ39 will be considered as met if all of the 3 previous tested contrasts (primary endpoint and 1st secondary endpoint) as well the two contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 2nd secondary endpoint will all be met (total of 5 contrasts) at a two-tailed alpha level of 5% each.
The statistical model to be used for the analysis of the change from baseline to Week 12/Treatment Termination visit in the Total PDQ39 will be an analysis of covariance (SAS® MIXED procedure) and the model will include treatment group, CGR and baseline PDQ39 score. The change from baseline to Week 12/Treatment Termination will be used as response variable in the model and differences between P2B001 0.6/0.75mg to its 2 individual components at Week 12/Treatment

Termination will be tested using 2 contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg and P2B001 0.6/0.75mg vs. rasagiline 0.75mg.

15.6.10.3 Change from Baseline to Week 12/Treatment Termination in the ADL UPDRS (part II)

The 3rd secondary endpoint, namely, the change from baseline to Week 12/Treatment Termination in the ADL UPDRS (part II) score will be considered as met if all of the 5 previous tested contrasts (primary endpoint, 1st and 2nd secondary endpoints) as well the two contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 3rd secondary endpoint will all be met (total of 7 contrasts) at a two-tailed alpha level of 5% each.
The statistical model to be used for the analysis of the change from baseline to Week 12/Treatment Termination in the ADL UPDRS (part II) will be a Mixed Model for Repeated Measures (MMRM) (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical week in trial by treatment interaction, CGR, and baseline ADL UPDRS (part II). 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 changes form baseline to post-baseline visits (weeks 5, 8 and 12) collected from all subjects randomized into the study will be used as response in the model.
The difference between P2B001 0.6/0.75mg to its 2 individual components at Week 12/Treatment Termination will be tested using 2 contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg and P2B001 0.6/0.75mg vs. rasagiline 0.75mg.

15.6.10.4 Change from Baseline to Week 12/Treatment Termination in the Motor UPDRS (part III) Score

The 4th secondary endpoint, namely, the change from baseline to Week 12/Treatment Termination in the motor UPDRS (part III) score will be considered as met if all of the 7 previous tested contrasts (primary endpoint, 1st, 2nd and 3rd secondary endpoints) as well the two contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 4th secondary endpoint will all be met (total of 9 contrasts) at a two-tailed alpha level of 5% each.
The statistical model to be used for the analysis of the change from baseline to Week 12/Treatment Termination in the Motor UPDRS (part III) will be a Mixed Model for Repeated Measures (MMRM) (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical week in trial by treatment interaction, CGR, and baseline Motor UPDRS (part III). 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 changes form baseline to post-baseline visits (weeks 5, 8 and 12) collected from all subjects randomized into the study will be used as response in the model.

The difference between P2B001 0.6/0.75mg to its 2 individual components at Week 12/Treatment Termination will be tested using 2 contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg and P2B001 0.6/0.75mg vs. rasagiline 0.75mg.

15.6.10.5 CGI-S Responder's Analysis at Week 12/Treatment Termination (change from baseline ≥1 CGI-S points)

The 5th secondary endpoint, namely, the CGI-S responder's analysis at Week 12/Treatment Termination (change from baseline ≥1 CGI-S points) will be considered as met if all of the 9 previous tested contrasts (primary endpoint, 1st, 2nd, 3rd and 4th secondary endpoints) as well the two contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg once daily and, P2B001 0.6/0.75mg vs. rasagiline 0.75mg once daily in the 4th secondary endpoint will all be met (total of 11 contrasts) at a two-tailed alpha level of 5% each.
A subject with an improvement of 1 point or more at Week12/Treatment Termination as compared to baseline will be classified as a "Responder" while other randomized subjects not falling into this definition will be classified as a "Non-Responders".

The analysis of this binary end-point will be based on estimating 2 contrasts (2 contrasts: P2B001 0.6/0.75mg vs. pramipexole 0.6mg and P2B001 0.6/0.75mg vs. rasagiline 0.75mg) derived from a baseline-adjusted, Logistic Regression model [SAS® PROC GENMOD with DIST=BIN and LINK=LOGIT] to this binary outcome measure. In addition to the treatment group the model will include the following covariates: CGR and baseline CGI-S. The treatment effect (odds-ratios) of P2B001 0.6/0.75mg vs its 2 individual components at Week 12/Treatment Termination on the proportion of responders at Week 12/Treatment Termination and the corresponding adjusted proportions will be displayed. In addition, the number and proportion of responders at Week 12/Treatment Termination will be displayed by treatment group. Exploratory Efficacy Endpoints
Analyses of the exploratory endpoints will provide additional insight into the therapeutic effect of P2B001 0.6/0.75. These endpoints will be tested for the ITT analysis set using the nominal alpha level of 5% without controlling for multiplicity. Detailed statistical methodology to be used for the analyses of these exploratory endpoints will be provided in a more detailed SAP to be developed while the study is ongoing and prior to locking the database and unblinding.

15.6.11 The exploratory endpoints to be analyzed are:

- To evaluate the efficacy of P2B001 0.6/0.75 mg compared to its individual components in the following endpoints:
  - Change from baseline to Week 12/Treatment Termination visit in each of the 8 PDQ39 subscales scores.
  - Change from baseline to Week 12/Treatment Termination visit in Health-Related Quality of Life (HRQOL) SF-12v2 questionnaire.

- Clinical Global Impression of Improvement (CGI-I) at Week 12/Treatment Termination visit.

- 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 at Week 12/Treatment Termination.
  - Proportion (%) of patients with ESS Score ≤10 at baseline and ESS score >10 at Week 12/Treatment Termination.
  - 3-Months rate of total number of adverse events.
  - Change from baseline to Week 12/Treatment Termination 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 from baseline to Week 12/Treatment Termination visit in the Orthostatic Hypotension Symptoms Assessment (OHSA) question 1.

- 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).

15.7 Safety Assessments

All safety assessments will use the Safety Analysis Set (ST) which includes all randomized subjects who were administered at least one study dose, according to the treatment actually received. The ST analysis set will serve as the principal analysis set for safety assessment. Safety analyses will exclude measurements taken 30 days after study treatment discontinuation as well as adverse events initiated 30 days after study treatment discontinuation.

15.7.1 Adverse Events

Adverse events will be recorded from the time a subject has signed the Informed Consent Form until the end of subject's study participation, including up to Week 14 Follow-Up visit, regardless of study IP administration.

The MedDRA dictionary will be 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:

- As analysis of AEs can incorporate only coded AEs, it is mandatory that at the time of database lock all AEs will be coded.
- Adverse events analyses will include only the Treatment Emergent Adverse Events (TEAEs), namely, those events which started at the time of first study IP administration or afterwards. AEs lacking start day or AEs recorded on day of first study IP lacking start time will be considered as TEAE.

The following analyses are pre-planned for adverse events:

- The incidence (no. of patients) and frequency (no. of events) of most frequent TEAEs (>5% of subjects in at least one study arm) by Preferred Term (PT).
- The incidence (no. of patients) and frequency (no. of events) of TEAEs broken down by System Organ Class (SOC) and PT.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs by SOC and PT in Subjects Early Discontinued from Study/Treatment.
- The incidence (no. of patients) and frequency (no. of events) of serious TEAEs by SOC and PT
- The incidence (no. of patients) and frequency (no. of events) of TEAEs when broken down by severity.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs broken down by relationship to study IP.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs when broken down by action taken with study IP.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs when broken down by event outcome.
- Adverse Events dictionary used to code Investigator's verbatim terms will be provided.
- Individual subject listings of all SAEs, treatment emergent SAEs, TEAEs and non-TEAEs.

15.7.2 Laboratory Tests

Analyses of safety central laboratory data will be performed in the following manner:

- The more detailed SAP to be developed while the study is ongoing and prior to locking the database and unblinding will provide quantitative criteria used to define the potentially clinically significant (PCS) abnormal laboratory values. Measurements to be used in the analysis are those taken only after the initiation of the 1st study IP administration. The incidence tables of PCS lab values as well as the individual subject listing will be provided. Please note that the denominator to be used for calculating percentages is the number of subjects with at least one measurement post initiation of the 1st study IP administration.

- Quantitative laboratory measurements will be categorized with reference to the normal ranges as Low, Normal or High. The incidence (no. of subjects) of abnormal values at any time post initiation of the 1st study IP administration, calculated for subjects with normal values at baseline will be provided. Analysis will include, per tested parameter, those subjects with normal baseline and at least one post-treatment measurement. Summary table will display the number and relative percentage of subjects with at least one abnormal value (above upper or below the lower normal range) at any time post initiation of the 1st study IP administration.
- Quantitative laboratory measurements will be categorized with reference to the normal ranges as Low, Normal or High. Shift analysis of the categorical change from baseline to each scheduled visit and to the last observed value will be provided. In case of sporadic repeated measurement within a visit, the last measurement per visit will be used to represent subject's value in the analysis.

Box-Plots of measurements done and figures of mean values ± SEs as well as descriptive statistics for all laboratory quantitative parameters and changes from baseline will be provided by scheduled visits and treatment groups. In case of sporadic repeated measurement within a visit, the last measurement per visit will be used to represent subject's value in the analysis.

15.7.3 Vital Signs

Analyses of vital signs will be performed in the following manner:

- The more detailed SAP to be developed while the study is ongoing and prior to locking the database and unblinding will provide quantitative criteria used to define the potentially clinically significant (PCS) abnormal values. Measurements to be used in the analysis are those taken immediately following the first administration of the study IP and onwards. The incidence tables of PCS values as well as the individual subject listing will be provided. The denominator to be used for calculating percentages is the number of subjects with at least one observation post 1st study IP administration.
- Box-Plots of measurements done, figures of mean values ±SEs as well as descriptive statistics for all parameters and changes from baseline (derived) will be provided by scheduled visits and treatment groups. Please note that the last measurement per visit will be used to represent subject's value in the analysis in case of sporadic repeated measurement within a visit.

15.8 ECG

The incidence of abnormal ECG findings will be presented by treatment group. Shift analysis from baseline will be provided as well.

15.9 Columbia Suicide Severity Rating Scale (CSSRS)

The Columbia Suicide Severity Rating Scale Screening/Baseline Version (CSSRS-BL) will be taken at screening. The Columbia Suicide Severity Rating Scale Since Last Visit (CSSRS-SLV) was to be taken at baseline and in all subsequent study visits.

Any positive answer to its behavior subcomponents at screening or baseline will identify a subject as with "Suicidal Behavior at Baseline". Similarly, any positive answer to it's the ideation subcomponents at any of these two visits will identify 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". Similarly, any positive answer to its behavior subcomponents in any of the post-dosing visits will identify a subject as with "Suicidal Behavior Post Dosing". Similarly, any positive answer to it's the ideation subcomponents in any of the post-randomization visits will identify a subject as with "Suicidal Ideation Post Dosing". A subject identified with either "Suicidal Behavior Post Dosing" or with "Suicidal Ideation Post Dosing" was also classified as with "Suicidal Behavior or Ideation Post Dosing".

The distribution of the number of subjects by these classifications post-dosing as well as shift analysis from baseline will be displayed. In addition, for the CSSRS-SLV, listing of Post First Study Dose CSSRS (Ideation) Grade 4 and 5 / Suicidal Behavior will be provided.

15.10 Tolerability Assessments

Tolerability analysis will be based on the number (%) of subjects who discontinued the study treatment early and the number (%) of subjects who discontinued study treatment early due to adverse events. Time to withdrawal will be presented by Kaplan-Meier curves.

15.11 Exploratory Safety Endpoint

Exploratory comparison between P2B001 0.6/0.75 mg and Pramipexole ER at Week 12/Treatment Termination will be performed in the following safety endpoints:

- Change from baseline to Week 12/Treatment Termination in the ESS score > 10.
- Adverse event frequency
- Change from baseline to Week 12/Treatment Termination in the differences in systolic and diastolic blood pressure measured during supine and standing positions.
- Comparison of percentage of patients presenting with sleepiness/drowsiness related AE's.
- Comparison of percentage of patients presenting with gastrointestinal (GI) adverse events.
- Comparison of percentage of patients presenting with neurological adverse events.
- Change from baseline to Week 12/Treatment Termination visit in the Orthostatic Hypotension Symptoms Assessment (OHSA) question 1.

15.12 Safety assessment scales

Results of scale assessments of daytime sleepiness, suicidality, and impulse control behaviors will be presented by study group

15.13 Statistical Analysis Plan (SAP)

A more detailed SAP will be developed while the study is ongoing and prior to locking the database and unblinding.

If ever there is a discrepancy between the Protocol and the Statistical Analysis Plan, the methods defined in the SAP will have precedence.

16 STUDY PERSONNEL

16.1 Study Site

At each study center the staff will consist of a minimum of one Principal Investigator and a clinical coordinator. If the Principal Investigator at a study center is not a neurologist, then the study center will need at least one sub-Investigator who is a neurologist. The neurologist will:
Verify subject eligibility (including diagnosis of early PD and UPDRS part III) at Visits 1 and 2
Perform complete physical and neurological examinations at Visit 1 and symptom-directed physical and neurological examination at visit 7 and unscheduled visits.

The neurologist will also decide on the dose of Pramipexole ER (or matching placebo) during the titration phase based on subject reporting of efficacy and tolerability. This will be done by a study visit at the end of week 3, and a phone call or an unscheduled visit at the end of week 4. The Pramipexole ER (or matching placebo) dose will be evaluated again at the end of week 5 as part of the activities done in study visit 4.

Assess Clinical Global Impression- Severity at Visits 2 and 6.
Assess Clinical Global Impression- Improvement at Visits 4, 5 and 6.
Perform UPDRS part III at Visits 1, 2, 4, 5 and 6 or the Site PI may delegate this responsibility to other senior trained research staff with at least 10 years' experience in conducting the UPDRS
All other study procedures can be conducted by the Principal Investigator, Clinical Coordinator or other member of the clinical staff with the relevant experience and who the PI has delegated to perform those procedures.

16.1.1 The Principal Investigator

The Principal Investigator (PI) will have overall responsibility to lead the site study team and all aspects of the study. The PI will oversee the accrual of appropriate subjects, the conduct of the study according to the trial protocol, communication with the IRB/EC, and the collection of required data.

16.1.2 The Clinical Coordinator or designee

The clinical coordinator or designee, as delineated on the Personnel Delegation Log, will be responsible for subject scheduling; completing and reviewing all subjects' case report forms and other documents and recording of adverse events as well as drug accountability. He/she will instruct the subject on proper study drug administration and completion of study scales

(including follow-up phone calls to the subject to obtain missing data from subject efficacy or safety scales completed at the previous visit). He/she will instruct the subject on proper study drug dosing. During the titration phase at the end of Weeks 1, 2 and 6 he/she will make a phone call to the subject to assure proper study dosing in the past week and remind of the dosing regimen for the next week.
He/she will collect and forward blood samples and requests to the appropriate laboratories, will obtain and forward laboratory results and will assist the Investigator.

16.2 The Sponsor

Pharma Two B
3 Pekeris st. Weizmann science park
Rehovot 7670203 Israel
Tel: 972 8 9462672
Fax: 972 8 9366832
Email: David@pharma2b.com

The sponsor will provide the following:

- Final protocol
- Study medication
- Drug Distribution
- Insurance for product liability

16.3 CRO

Name: PRA Health Science
Address: 4130 ParkLake Avenue - Suite 400 Raleigh,
North Carolina 27612
Tel: +1 (919) 786-8200
Fax: +1 913.890.5969

The CRO commissioned by Pharma Two B will assist in the conduct and analysis of the trial. The CRO will be responsible for the following:

- Project management
- Clinical operation
- Drug safety plan and reporting
- Study specific training
- Data management
- Monitoring
- Quality Assurance
- Final clinical report

- Central laboratories

16.3.1 CRO Clinical Trials Manager

The CRO Clinical Trials Manager is responsible for all aspects of the study including the proper design and conduct, and day-to-day activities of the study and to ensure that the sponsor supplies adequate resources to provide high quality study management, monitoring and data management. The Corporate Clinical Trials Manager will represent the sponsor on the study various Committees:
Name: Lysander Stemmerik or designee
Address: PRA Health Science, WTC Papendorp, Papendorpseweg 100, 3528 BJ Utrecht , The Netherlands .
Tel: +31 50.850.5749
Email; StemmerikLysander@prahs.com

The CRO will be responsible for review of all Serious Adverse Events (SAEs) to ensure that each SAE is adequately described to allow determination of deportability to the Regulatory Authorities.

16.3.2 Statistics and Data Management Centers (S&DM)

The CRO's lead data manger is responsible for data management of electronic CRF's. Statistical analyses will be performed by StatExcellence Ltd., Israel.

16.3.3 Medical Monitor

The Medical Monitor is responsible to periodically review the safety data in a blinded fashion to include AEs, vital signs, ECG and laboratory values. A consistency check of safety and efficacy variables will be performed.

16.3.4 Local Clinical Trial Manager (LCTM)

The LCTM based at CRO subsidiaries, is responsible for the local day-to-day activities of the study and to ensure that the sponsor supplies adequate resources to provide high quality study management, monitoring and data management. The LCTM is responsible for submitting all safety reports to local regulatory authorities and to Investigators, as required. The LCTM supervises the monitoring activities.

16.3.5 Clinical Research Associate

Clinical Research Associate (CRA, monitor) is responsible for monitoring visits. These visits will be arranged in advance, at a mutually acceptable time, with site personnel. Sufficient time

must be allowed by the site personnel for the Monitor to review the relevant source documents. The coordinator and/or Investigator(s) should be available to answer questions or resolve data clarifications. Adequate time and space for these visits should be made available by the Investigator. The monitor will review, on a regular basis, the progress of the study with the Investigator and other site personnel and check completeness and blind maintenance. The monitor will verify the data entered into the eCRF for accuracy and completeness. At the end of the study, a close-out monitoring visit will be performed.

16.4 Study Committees

16.4.1 Data & Safety Monitoring Board (DSMB)

The DSMB is intended to assist and consult on any safety aspects to ensure the safety of study subjects. Pharma Two B with the study CRO (PRA Health Science) will be responsible to select DSMB members among different experts in the field. The committee will review, periodically, in unblinded fashion, all safety data accumulated in the study. The committee will document all their recommendations which will be provided to the sponsor and the CRO.

16.4.2 Subject Central Eligibility Monitoring Committee (EMC)

After the Investigator has determined a subject has met all of the inclusion criteria and none of the exclusion criteria but before randomizing the subject via RTSM, the Investigator will need to complete a randomization authorization form (RAF) for that subject and e-mail it to the EMC, which consists of expert Parkinson's disease neurologists. Upon receipt of the RAF, the EMC will review the provided information to confirm the subject's eligibility for the study. Only after receiving confirmation from the EMC that the subject meets eligibility criteria via a signed RAF, may the Investigator randomize the subject using the RTSM system.
The EMC may also reject the inclusion of a subject due to that subject not meeting eligibility criteria. Any rejection will be explained to the Investigator via email.

17 REGULATORY AND ETHICAL ISSUES

17.1 Compliance with Regulations Applicable to Clinical Trials

The study will be conducted according to the protocol, the laws, regulations and administrative provisions relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use, as applicable by national legislation and directives, including Directive 2001/20/EC of the European Parliament and the Council of the European Union and US 21 CFR Part 11, 50, 54, 56 and 312.

17.2 Informed Consent

The principles of informed consent, according to Declaration of Helsinki 1964 and all its updates, the International Conference on Harmonization (ICH) step 5 guidelines on Good Clinical Practice (GCP), 21 CFR part 50 of the FDA Regulations and/or EU Directives, will be followed. A subject should not enter a clinical study or perform any study-related procedures until subject has been properly informed, has been given time to contemplate participation, and has freely given his/her consent by signing and dating the EC/IRB approved informed consent form.
The proposed consent form and any other documents relevant to the consent process must be submitted to the EC/IRB together with the protocol and must be approved prior to study start.
A signed copy of the consent form will be given to the subject and the original will be maintained at the site following the signing and dating by the person administering the consent and witness (where appropriate).

17.3 Ethics Committee (EC) / Institutional Review Board (IRB)

The study must have unconditional approval in writing, by an appropriate Ethics Committee/Institutional Review Board (EC/IRB). A copy of the Letter of Approval from the EC/IRB, which contains specific identification of the documents approved, must be received by the sponsor prior to site initiation.
Any substantial amendments to the protocol or subsequent changes to the informed consent form as a result of changes to the protocol and/or Investigator's Brochure that is approved by the sponsor, must also be sent to the EC/IRB and written opinion has to be provided to the sponsor.
Records of the EC/IRB review and opinion of all documents pertaining to this study must be kept on file by the Investigator and are subject to regulatory authority and/or sponsor inspection during or after completion of the study.
Serious Adverse Events (SAEs) must also be reported to the EC/IRB by the Investigator or the sponsor.
Periodic status reports must be submitted to the EC/IRB as required, as well as notification of completion of the study and a final report where applicable. A copy of all reports submitted to the EC/IRB must be sent to the sponsor.

17.4 Protocol Amendments

Changes to the protocol should only be made by an approved protocol amendment. Protocol amendments must be approved by the sponsor and each respective site’s EC/IRB prior to implementation.
For clinical trial sites located in EU member states, the procedures outlined in Directive 2001/20/EC, Article 10(a), are applicable. Elsewhere, the country regulations apply.

17.5 Subject Confidentiality

All subject data will be identified only by a subject identification number, subject initials and date of birth. The subject's personal data (e.g. name and address) will be blinded correspondingly in all data analyses. However, after receiving the subject's approval (by signing the Informed Consent), it is required that the Investigator permit the study monitor, independent auditor or regulatory agency personnel (with or without the Investigator) to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical history to verify eligibility; laboratory test result reports; admission/ discharge summaries for hospital admissions occurring while the subject is in the study; and autopsy reports for deaths occurring during the study (where available).

The subject's authorization allows the sponsor to receive and review the subject's protected health information which may be re-disclosed to any authorized representative of the sponsor or central laboratory facility for review of subject medical records in the context of the study.

17.6 Liability and Insurance

A Certificate of Clinical Trials Insurance will be provided to the study centers by the sponsor upon request.

18 DOCUMENTATION

18.1 Study File and Site Documents

Prior to the initiation of the study, the following documents must be received by the sponsor from the study site:

- Confidential Disclosure Agreement
- Signed protocol, amendments and notifications (if applicable) pages by the Principal Investigator.
- The Principal Investigator curriculum vitae and where required current medical license.
- Signed Clinical Study Agreement.
- EC/IRB membership list or an official statement that the EC/IRB is in compliance the local regulations.
- EC/IRB written opinion for the protocol, amendments, informed consent, subject information sheet (if applicable), advertisements (if applicable).

18.2 Site Documents/Equipment Supplied by the Sponsor

Prior to the initiation visit of the study, the sponsor will supply the site Investigator with the following items, in addition to the protocol:

- Current version of the Investigator's Brochure or equivalent as agreed with the regulatory authority.

- Regulatory Binder including all study related forms
- Informed Consent Template
- Insurance Certificate

18.3 Maintenance and Retention of Records

The Investigator will get from the sponsor an essential documents binder EDB or set up a Site Master File (SMF) at the beginning of the study. It will be the responsibility of the Investigator and study staff to maintain a comprehensive and centralized filing system of all documents relevant to the study.

These documents include:

- Subject Files (Source documents) – substantiating the data entered in the eCRF with regards to laboratory data, subject histories, treatment regimens, etc.
- Subject Exclusion records – reflecting the reasons any subject was screened for the study and found to be ineligible.
- Drug Dispensing Log – reflecting the total amount of medication received and returned to the sponsor, and the amounts administrated to the subject. This information should agree with the information entered in the eCRF.
- Informed Consent Forms (ICF) – will be available for each subject and will be verified for proper documentation.
- Study Notes – this section of the eCRF is used to explain any aspect of the study that is not easily entered on the routine eCRF, and could include items such as:
- Deviations from the protocol; nature, reasons and approval by the Investigator.
- Comments or explanations of unusual findings.
- Any data or clarification of data not explicitly requested on the eCRF.

The EDB or SMF will be stored in a secure but accessible manner. The essential documents will be legible and accurate. The participating centers will keep copies of relevant documents, including essential center-specific documents. Essential documents should be retained until at least 2 years after the approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational product. These documents should be retained for a longer period, however if required by the regulatory requirements or by informing the Investigator/institution as to when these documents no longer need to be retained.

The EDB orSMF will be archived by the Sponsor for a minimum of 15 years following the signing of the clinical report.

- Site Investigators will be instructed to retain all study records required by the sponsor and regulatory authorities in a secure and safe facility

with limited access for at least 15 years or longer if required by local regulations.

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

18.4 Data Handling

An Electronic Data Capture (EDC) system to collect subject electronic Case Report Form (eCRF) information will be used. All the information collected during the study will be recorded in the eCRF identified by subject initials and subject ID number, for each subject enrolled, including those removed for any reason after administering the first dose. It is the responsibility of the Investigator and sub-Investigator to ensure that the eCRFs are properly and completely filled in.

Central data management will be performed by PRA. Internet-based remote data capture will be used for entering, managing, and validating data from centers. The following regulation will be followed:

- FDA 21CRF part 11 rule
- ICH, Good Clinical Practice, Consolidated guideline
- FDA Guidance for Industry “Computerized system used in clinical trials.
- EU Directives

Data will be entered at the site by the site Investigator, study coordinator or the site coordinator, onto the eCRF.

The eCRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore, the eCRFs must be completed for each subject screened and enrolled according to the subject’s source data on a per-visit basis. For screen failures, only date of screening, date of screen failure, subject demographics and inclusion/exclusion criteria not met will be recorded within EDC. Any adverse events for screen failures that occur after signing the ICF will be captured only in the source documents and not in the eCRF.

Subjects should not be identified by name. Appropriately coded identification and subject initials must be used. The site Investigator must keep a separate log of subject names and addresses (i.e. Subject Identification Record).

All data collected in the eCRF must be approved by the site Investigator or designee and can be verified against the subject’s source documents by the monitor, according to the monitoring plan.

18.4.1 Source Documents

Prescription forms, label logs, laboratory test results, ECG strips and all other source documents should be maintained and kept at the study site in the subject's study binder. If the hospital file is

an electronic system (computerized database), all data should be printed out, signed and dated by the Investigator.

19 STUDY MONITORING

19.1 Monitors and Monitoring Visits

The Study monitor/CRA will be responsible for ensuring adherence to local regulations, EU Directives (where applicable), ICH guidelines and the sponsor's SOPs. Study monitors for this trial will be provided by the sponsor or sponsor's designee. The monitors will operate according to the EU Directives and in compliance with ICH guidelines, as well as local regulations. Monitors will be trained to monitor the study. They will be trained on ICH GCP guidelines, study protocol.

Regular monitoring of study data at the site will be performed in accordance with applicable regulations and according to a study specific monitoring plan. The site will be monitored to ascertain that enrollment rate, data recording and protocol adherence are satisfactory. The frequency of monitoring the site may fluctuate depending upon enrollment rate and the quantity of data collected.

The monitor will review the maintenance of regulatory documentation and Study Drug accountability. The monitor will review the progress of the study with the site Investigator and other site personnel on a regular basis. At the end of the study, a close-out monitoring visit will be performed. Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitor to review eCRFs and relevant source documents or resolve data clarifications. Adequate time and space for these visits will be made available by the site Investigator.

19.2 Primary Source Documents

The site Investigator must maintain primary source documents supporting eCRF data entries. These documents, which are considered "source data", should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the subject is being studied
- General information supporting the subject's eligibility to participate in the study
- Medical history, physical and neurological findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the site Investigator(s); occurrence (or lack) of AEs; and changes in

medication usage, including the date the IMP was commenced and completed
- Drug dispensing
- Vital signs
- Subject evaluation scales
- Any additional visits during the study
- Any relevant telephone conversations with the subject regarding the study, subject's satisfaction and tolerability of the treatment during titration phase or possible AEs
- Original, signed informed consent forms for study participation

The site Investigator must also retain all subject-specific printouts, reports of tests and procedures performed as a requirement of the study. During monitoring visits, the monitor will need to verify data in the eCRFs against these source data.

20 USE OF INFORMATION AND PUBLICATION

20.1 Confidential Information

All information supplied by the sponsor in association with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, eCRFs and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of the sponsor, shall not be disclosed to others without the written consent of the sponsor and shall not be used except in the performance of this study.
The information developed during the conduct of this clinical study is also considered confidential, and will be used by the sponsor in connection with the development of P2B001. The information may be disclosed as deemed necessary by the sponsor. To allow the use of the information derived from this clinical study, the site Investigator is obliged to provide the sponsor with complete test results and all data developed in this study. Should the Investigator wish to publish the results of this study, the Investigator agrees to provide the sponsor with a manuscript for review 60 days prior to submission for publication. The sponsor retains the right to delete from the manuscript confidential information and to object to suggested publication and/or its timing (at the sole discretion of the sponsor).

21 INVESTIGATOR AGREEMENT

I have carefully read the foregoing protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current GCP regulations and will attempt to complete the study within the time designated.

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

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

_____
Principal Investigator's name

_____
Signature

_____
Date

_____
Institution

22 APPENDICES

22.1 Appendix I: Schedule of Activities:

Visit Number	1	2	3	****	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						

Visit Number	1	2	3	****	4	5	6	7
Visit Type	**Screening**	**Baseline**	**End of Week 3**	**End of Week 4**	**End of Wee k 5**	**End of Week 8**	**End of Wee k 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**
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
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

22.2 Appendix II: Laboratory Tests

- Hematology (will be performed on screening visit, and visit 7 safety follow up visit): White Cell and Differential Count, Red Cell Count, Hemoglobin, Hematocrit, Mean Cell Volume, Mean Cell Hemoglobin, Mean Cell Hemoglobin Concentration and Platelet Count.
- Clinical Chemistry (will be performed on screening and visit 7 safety follow up visit):
  Sodium
  Potassium
  Chloride
  Glucose
  BUN
  Creatinine
  Calcium
  Phosphate
  Bilirubin
  Alkaline Phosphatase
  Gamma glutamyl transpeptidase (Gamma GT)
  Aspartate transaminase (SGOT; AST)
  Alanine transaminase (SGPT; ALT)
  Total protein
  Albumin
  Cholesterol
- Urinalysis (will be performed on screening, and safety follow up visit): pH, Protein, Glucose, Ketones, Urine microscopic: White Blood Cell Count, Red Blood Cell Count, Casts.
- Coagulation (will be performed at screening to determine eligibility and at visits 4 and 5 for subjects with mild hepatic impairment to determine compliance with exclusion criteria): PT/INR – prothrombin time and ratio as well as aPTT.

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

Serum pregnancy test at screening and safety visit . Urine pregnancy test at baseline visit. (Minimum sensitivity 25 IU/L or equivalent units of β-HCG).

22.3 Appendix III: The Epworth Sleepiness Scale (ESS)

How likely are you to doze off or fall asleep in the situations described below, in contrast to feeling just tired?
This refers to your usual way of life in recent times.
Even if you haven't done some of these things recently try to work out how they would have affected you.
Use the following scale to choose the most appropriate number for each situation:-

0 = would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation Chance of dozing
Sitting and reading . . . . . .
Watching TV . . . . . .
Sitting, inactive in a public place (e.g. a theatre or a meeting) . . . . . .
As a passenger in a car for an hour without a break . . . . . .
Lying down to rest in the afternoon when circumstances permit . . . . .
Sitting and talking to someone . . . . . .
Sitting quietly after a lunch without alcohol . . . . . .
In a car, while stopped for a few minutes in the traffic . . . . . .

22.4 Appendix IV: Clinical Global Impression - Severity

The Clinical Global Impression – Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness (Parkinson's Disease) at the time of assessment relative to the clinician's past experience with patients who have the same diagnosis as one of the following:

0 = not assessed
1 = normal;
2 = borderline ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill patients

22.5 Appendix V: OHAS question 1 (Kaufmann H, 2012)

Question 1: “Dizziness, lightheadedness, feeling faint or feeling as though you might pass out"”

Please circle the number on the scale (where 0 = None and 10 = Worst Possible) that best rates how severe your symptoms from low blood pressure have been on average **over the past week**. If you have not experienced the symptom, circle zero (0). PLEASE RATE THE SYMPTOMS THAT ARE DUE ONLY TO YOUR LOW BLOOD PRESSURE PROBLEM.

22.6 Appendix VI: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease rating Scale (QUIP-RS)

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-RS version). The questionnaire should be completed according to the past 4 weeks.

1. How much do you think about the following behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)?
Gambling? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Sex? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Buying? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Eating? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Performing tasks or hobbies? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Repeating simple activities? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Taking your PD medications? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
2. Do you have urges or desires for the following behaviors that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in them)?
Gambling? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Sex? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Buying? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Eating? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Performing tasks or hobbies? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Repeating simple activities? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Taking your PD medications? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
3. Do you have difficulty controlling the following behaviors (such as increasing them over time, or having trouble cutting down or stopping them)?
Gambling? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Sex? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Buying? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Eating? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Performing tasks or hobbies? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Repeating simple activities? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Taking your PD medications? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
4. Do you engage in activities specifically to continue the following behaviors (such as hiding what you are doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?
Gambling? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Sex? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Buying? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)

Eating? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Performing tasks or hobbies? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Repeating simple activities? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)
Taking your PD medications? ___Never(0) ___Rarely(1) ___Sometimes(2) ___Often(3) ___Very often(4)

22.7 Appendix VII: Health-Related Quality of Life (HRQOL) SF-12v2

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

3. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

22.8 Appendix VIII: Columbia Suicide Severity Rating Scale (CSSRS)

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

1. Wish to be Dead

Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.

Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

2. Non-Specific Active Suicidal Thoughts

General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.

Have you actually had any thoughts of killing yourself?

If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*

Have you been thinking about how you might do this?

If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*

Have you had these thoughts and had some intention of acting on them?

If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent

Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.

Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Frequency

How many times have you had these thoughts?

(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration

When you have the thoughts, how long do they last?

(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability

Could/can you stop thinking about killing yourself or wanting to die if you want to?

(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents

Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?

(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?

(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

SUICIDAL BEHAVIOR
(Check all that apply, so long as these are separate events; must ask about all types)

Actual Attempt:
A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.
Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.
Have you made a suicide attempt?
Have you done anything to harm yourself?
Have you done anything dangerous where you could have died?
- ***What did you do?***
- ***Did you_____ as a way to end your life?***
- ***Did you want to die (even a little) when you_____?***
- ***Were you trying to end your life when you _____?***
- ***Or did you think it was possible you could have died from_____?***

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent)
If yes, describe:

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

Interrupted Attempt:
When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*
Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.
Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?
If yes, describe:

Aborted Attempt:
When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.
Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?
If yes, describe:

Preparatory Acts or Behavior:
Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).
Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?
If yes, describe:

Suicidal Behavior:
Suicidal behavior was present during the assessment period?

Suicide:

Answer for Actual Attempts Only	M A D
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).	

22.9 Appendix IX: UPDRS (Fahn S, 1987)

The Unified Parkinson's Disease Rating Scale (UPDRS) is divided into five parts. In this study only parts II and III will be performed and their scores will be summarize (maximum sum of 160) . Part II, Activities of Daily Living (ADL) (for both "on" and "off") (questions 5-17) is also historical information. Part III (questions 18-31) is done as a motor examination at the time of a visit as defined in this protocol.
The various items to be rated are scored using a 5-point system (i.e., 0 is normal and 4 indicates a severe abnormality).

Part II: Activities of Daily Living (Score 0-4)

5) Speech
   0 - Normal
   1 - Mildly affected. No difficulty being understood.
   2 - Moderately affected. Sometimes asked to repeat statements.
   3 - Severely affected. Frequently asked to repeat statements.
   4 - Unintelligible most of the time

6) Salivation
   0 - Normal
   1 - Slight but definite excess of saliva in mouth; may have nighttime drooling
   2 - Moderately excessive of saliva; may have minimal drooling
   3 - Marked excess of saliva with some drooling
   4 - Marked drooling, requires constant tissue or handkerchief

7) Swallowing
   0 - Normal
   1 - Rare choking
   2 - Occasional choking
   3 - Requires soft food
   4 - Requires nasogastric tube or gastrotomy feeding

8) Handwriting
   0 - Normal
   1 - Slightly slow or small
   2 - Moderately slow or small; all words are legible
   3 - Severely affected; not all words are legible

4 - The majority of words are not legible

9) Cutting Food, Handling Utensils
0 - Normal
1 - Somewhat slow, but no help needed
2 - Can cut most foods, although clumsy and slow; some help needed
3 - Food must be cut by someone, but can still feed slowly
4 - Needs to be fed

10) Dressing
0 - Normal
1 - Somewhat slow, but no help needed
2 - Occasional assistance with buttoning, getting arms in sleeves
3 - Considerable help required, but can do some things alone
4 – Helpless

11) Hygiene
0 - Normal
1 - Somewhat slow, but no help needed
2 - Needs help to shower or bathe, or very slow in hygienic care
3 - Requires assistance for washing, brushing teeth, combing hair, going to bathroom
4 - Foley catheter or other mechanical aids

12) Turning In Bed And Adjusting Bed Clothes
0 - Normal
1 - Somewhat slow and clumsy, but no help needed
2 - Can turn alone or adjust sheets, but with great difficulty
3 - Can initiate, but not turn or adjust sheets alone
4 – Helpless

13) Falling (Unrelated To Freezing)
0 - None
1 - Rare falling
2 - Occasionally falls, less than once per day
3 - Falls an average of once daily
4 - Falls more than once daily

14) Freezing When Walking
0 - None

1 - Rare freezing when walking; may have start-hesitation
2 - Occasional freezing when walking
3 - Frequent freezing. Occasionally falls from freezing
4 - Frequent falls from freezing

15) Walking
0 - Normal
1 -Mild difficulty. May not swing arms or may tend to drag leg
2 - Moderate difficulty, but requires little or no assistance
3 - Severe disturbance of walking, requiring assistance
4 - Cannot walk at all, even with assistance

16) Tremor
0 - Absent
1 - Slight and infrequently present
2 - Moderate; bothersome to patient
3 - Severe; interferes with many activities
4 - Marked; interferes with most activities.

17) Sensory Complaints Related To Parkinsonism
0 - None
1 - Occasionally has numbness, tingling or mild aching
2 - Frequently has numbness, tingling or aching; not distressing
3 - Frequent painful sensations
4 - Excruciating pain

PART III: Motor Examination (score 0-4)
18) Speech
0 - Normal
1 - Slight loss of expression, diction and/or volume
2 - Monotone, slurred but understandable; moderately impaired
3 - Marked impairment, difficult to understand -
4 – Unintelligible

19) Facial Expression
0 - Normal
1 - Minimal hypomania, could be normal “Poker Face”
2 - Slight but definitely abnormal diminution of facial expression
3 - Moderate hypomania; lips parted some of the time

4 - Masked or fixed faces with severe or complete loss of facial expression ; lips parted 1/4 inch or more

20) Tremor at Rest

Face, lips and chin

0 - Absent

1 - Slight and infrequently present

2 - Mild in amplitude and persistent; or moderate in amplitude, but only intermittently present

3 - Moderate in amplitude and present most of the time

4 - Marked in amplitude and present most of the time

Right hand

0 - Absent

1 - Slight and infrequently present

2 - Mild in amplitude and persistent; or moderate in amplitude, but only intermittently present

3 - Moderate in amplitude and present most of the time

4 - Marked in amplitude and present most of the time

Left hand

0 - Absent

1 - Slight and infrequently present

2 - Mild in amplitude and persistent; or moderate in amplitude, but only intermittently present

3 - Moderate in amplitude and present most of the time

4 - Marked in amplitude and present most of the time

Right foot

0 - Absent

1 - Slight and infrequently present

2 - Mild in amplitude and persistent; or moderate in amplitude, but only intermittently present

3 - Moderate in amplitude and present most of the time

4 - Marked in amplitude and present most of the time

Left foot

0 - Absent

1 - Slight and infrequently present

2 - Mild in amplitude and persistent; or moderate in amplitude, but only intermittently present

3 - Moderate in amplitude and present most of the time

4 - Marked in amplitude and present most of the time

21) Action or Postural Tremor Of Hands

Right

0 - Absent

1 - Slight; present with action

2 - Moderate in amplitude, present with action

3 - Moderate in amplitude with posture holding as well as action

4 - Marked in amplitude; interfere with feeding

Left

0 - Absent

1 - Slight; present with action

2 - Moderate in amplitude, present with action

3 - Moderate in amplitude with posture holding as well as action

4 - Marked in amplitude; interfere with feeding

22) RIGIDITY (Judged on Passive Movement of Major Joints with Subject Relaxed In sitting position. Cogwheeling to be ignored)

Neck

0 - Absent

1 - Slight or detectable only when activated by mirror or other movements

2 - Mild or moderate

3 - Marked, but full range of motion easily achieved

4 - Severe, range of motion achieved with difficulty

Right Upper Extremities

0 - Absent

1 - Slight or detectable only when activated by mirror or other movements

2 - Mild or moderate

3 - Marked, but full range of motion easily achieved

4 - Severe, range of motion achieved with difficulty

Left Upper Extremities

0 - Absent

1 - Slight or detectable only when activated by mirror or other movements

2 - Mild or moderate

3 - Marked, but full range of motion easily achieved

4 - Severe, range of motion achieved with difficulty

Right Lower Extremities
0 - Absent
1 - Slight or detectable only when activated by mirror or other movements
2 - Mild or moderate
3 - Marked, but full range of motion easily achieved
4 - Severe, range of motion achieved with difficulty

Left Lower Extremities
0 - Absent
1 - Slight or detectable only when activated by mirror or other movements
2 - Mild or moderate
3 - Marked, but full range of motion easily achieved
4 - Severe, range of motion achieved with difficulty

23) Finger Taps (Subject taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately)
Right hand
0 - Normal ≥ 15/5 sec)
1 - Mild slowing and/or reduction in amplitude (11-14.5 sec)
2 - Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement (7-10/5 sec)
3 - Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement (3-6/5 sec)
4 - Can barely perform the task (0-2/5 sec)

Left hand
0 - Normal ≥ 15/5 sec)
1 - Mild slowing and/or reduction in amplitude (11-14.5 sec)
2 - Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement (7-10/5 sec)
3 - Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement (3-6/5 sec)
4 - Can barely perform the task (0-2/5 sec)

24) Hand Movement (Subject opens and closes hands in rapid succession with widest amplitude possible, each hand separately)

Right
0 - Normal
1 - Mild slowing and/or reduction in amplitude
2 - Moderately impaired. Definite and early fatiguing. May have occasional arrests in movements
3 - Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement
4 - Can barely perform the task

Left
0 - Normal
1 - Mild slowing and/or reduction in amplitude
2 - Moderately impaired. Definite and early fatiguing. May have occasional arrests in movements
3 - Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement
4 - Can barely perform the task

25) Rapid Alternating Movements Of Hands (Pronation, supination movements of hands, vertically or horizontally with as large an amplitude as possible, both hands simultaneously)
Right
0 - Normal
1 - Mild slowing and/or reduction in amplitude
2 - Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement
3 - Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement
4 - Can barely perform the task
Left
0 - Normal
1 - Mild slowing and/or reduction in amplitude
2 - Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement
3 - Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement
4 - Can barely perform the task

26) Leg Agility (Subject taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 inches)

Right

0 - Normal

1 - Mild slowing and/or reduction in amplitude

2 - Moderately impaired. Definite and early fatiguing. May have occasional arrest in movement

3 - Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement

4 - Can barely perform the task

Left

0 - Normal

1 - Mild slowing and/or reduction in amplitude

2 - Moderately impaired. Definite and early fatiguing. May have occasional arrest in movement

3 - Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement

4 - Can barely perform the task

27) Arising From Chair (Subject attempts to arise from a straight-back wood or metal chair with arms folded across chest)

0 - Normal

1 - Slow, or may need more than one attempt

2 - Pushes self up from arms of seat

3 - Tends to fall back and may have to try more than one time, but can get up without help

4 - Unable to arise without help

28) Posture

0 - Normal erect

1 - Not quite erect, slightly stooped posture; could be normal for older person

2 - Moderately stooped posture, definitely abnormal, can be slightly leaning to one side

3 - Severely stooped posture with kyphosis; can be moderately leaning to one side

4 - Marked flexion with extreme abnormality of posture

29) Gait

0 - Normal

1 - Walks slowly, may shuffle with short steps, but no festination or propulsion

2 - Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion

3 - Severe disturbance, of gait requiring assistance

4 - Cannot walk at all, even with assistance

30) Postural Stability (Response to sudden posterior displacement

0 - Normal

1 - Retropulsion, but recovers unaided

2 - Absence of postural response; would fall if not caught by examiner

3 - Very unstable, tends to lose balance spontaneously

4 - Unable to stand without assistance

31) Body Bradykinesia And HypokinesIA (Combining slowness, hesitancy, decreased arm swing, small amplitudes and poverty of movement in general)

0 - None

1 - Minimal slowness, giving movement a deliberate character; could be normal for some person. Possibly reduced amplitude.

2 - Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 - Moderate slowness, poverty or small amplitude of movement

4 - Marked slowness, poverty or small amplitude of movement

22.10 Appendix X: Quality of Life - PDQ39

Please tick one box for each question.

Due to having Parkinson's disease, how often (never, occasionally, sometimes, often, always) during the last month have you:

1. Had difficulty doing the leisure activities which you would like to do?
2. Had difficulty looking after your home, e.g. DIY, house work, cooking?
3. Had difficulty carrying bags of shopping?
4. Had problems walking half a mile?
5. Had problems walking 100yards?
6. Had problems getting around the house as easily as you would like?
7. Had difficulty getting around in public?
8. Needed someone else to accompany you when you went out?
9. Felt frightened or worried about falling over in public?
10. Been confined to the house more than you would like?
11. Had difficulty washing yourself?
12. Had difficulty dressing yourself?
13. Had problems doing up your shoe laces?
14. Had problems writing clearly?
15. Had difficulty cutting up your food?
16. Had difficulty holding a drink without spilling it?
17. Felt depressed?
18. Felt isolated and lonely?
19. Felt weepy or tearful?
20. Felt angry or bitter?
21. Felt anxious?
22. Felt worried about your future?
23. Felt you had to conceal your Parkinson's from people?
24. Avoided situations which involve eating or drinking in public?
25. Felt embarrassed in public due to having Parkinson's disease?
26. Felt worried by other people's reaction to you?
27. Had problems with your close personal relationships?
28. Lacked support in the ways you need from your spouse or partner? (If you do not have a spouse or partner please mention)
29. Lacked support in the ways you need from your family or close friends?
30. Unexpectedly fallen asleep during the day?
31. Had problems with your concentration, e.g. when reading or watching TV?
32. Felt your memory was bad?
33. Had distressing dreams or hallucinations?

34. Had difficulty with your speech?
35. Felt unable to communicate with people properly?
36. Felt ignored by people?
37. Had painful muscle cramps or spasms?
38. Had aches and pains in your joints or body?
39. Felt unpleasantly hot or cold?

22.11 Appendix XI : UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Hughes AJ, 1992)

Step 1: Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following

Muscular rigidity

4-6 Hz rest tremor

postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2: Exclude other cause of Parkinson's

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3: Supportive prospective positive criteria for Parkinson’s disease

Three or more required for diagnosis of definite Parkinson’s disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

*From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson’s disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.

22.12 Appendix XII: Modified Hoehn & Yahr scale

The H&Y scale is a commonly used system for describing how the symptoms of Parkinson's disease progress. It was originally published in 1967 in the journal Neurology by Melvin Yahr and Margaret Hoehn. 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 indicate the relative level of disability.

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.

22.13 Appendix XIII: Mini-Mental State Examination (MMSE)

Instructions: Score one point for each correct response within each question or activity.
Questions
Orientation to Time
1. “What is the year? Season? Date? Day? Month?” 5 points
Orientation to Place
2. “Where are we now? State? County? Town/city? Hospital? Floor?” 5 points
Registration
3. Name 3 common objects (APPLE, TABLE and PENNY): Take 1 second to say each. Then ask the patient to repeat them after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all three. 3 points
Attention and Calculation
4. “Spell WORLD backwards.” (D-L-R-O-W) 5 points.
Recall
5.“Earlier I told you the names of three things. Can you tell me what those were?” 3 points
Naming
6. Show the patient two simple objects, such as a wrist watch and a pencil, and ask the patient to name them. 2 point.
Repetition
7. “Repeat the phrase: ‘No ifs, ands, or buts.’” 1 point
Comprehension
8. “Take the paper in your right hand, fold it in half, and put it on the floor.” (The examiner gives the patient a piece of blank paper) 3 points
Reading
9. “Please read this and do what it says.” (Written instruction is “Close your eyes.”) 1 point.
Writing
10. “Make up and write a sentence about anything.” (This sentence must contain a noun and a verb.) 1 point.
Copying
11. “Please copy this picture.” (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 1 point.
30 points total.
Sources:
• Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-198.

22.14 Appendix XIV: Clinical Global Impression - Improvement

The Clinical Global Impression =improvement (CGI-I) is a 7-point scale that requires the clinician to compares the patient's overall clinical condition after medication has been initiated to the one week period just prior to the initiation of medication use (baseline visit) as one of the following:

1=very much improved since the initiation of treatment
2=much improved
3=minimally improved
4=no change from baseline (the initiation of treatment)
5=minimally worse
6= much worse
7=very much worse since the initiation of treatment

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