Clinical trial results:
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.

Methodology: This was a randomised, placebo-controlled, double-blind, double-dummy study design with a 12-week treatment period. Eligible subjects with Parkinson's disease (PD) of less than 3 years' duration participated in a titration phase of up to 6 weeks, followed by a maintenance phase.
Subjects were randomised 2:2:2:1 into 1 of 4 treatment groups: P2B001 (a fixed low dose combination of pramipexole 0.6 mg [PPX] and rasagiline 0.75 mg [RAS]), PPX, RAS, or PramiER (the currently marketed version of pramipexole, extended release formulation).
Treatments were taken once daily: 1 capsule (P2B001, PPX, RAS, or placebo) plus 1-3 tablets (PramiER or placebo).
The study was conducted to evaluate the efficacy of the combined product P2B001 in comparison with its individual components (PPX and RAS) and to compare safety and efficacy with therapeutic doses of PramiER.

Summary

EudraCT number	2017-001420-21
Trial protocol	DE ES
Global end of trial date	24 August 2021

Results information

Result version number	v1 (current)
This version publication date	09 September 2022
First version publication date	09 September 2022

Trial information

Trial identification

Sponsor protocol code	P2B001/003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03329508
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharma Two B Ltd
Sponsor organisation address	3 Pekeris St., Weizmann Science Park, Rehovot, Israel, 7670203
Public contact	Irit Aish, Pharma Two B Ltd, 00972 89472672, irita@Pharma2b.com
Scientific contact	Hadas Friedmann, Pharma Two B Ltd, 00972 89472672, hadas@pharma2b.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 August 2021
Global end of trial reached?	Yes
Global end of trial date	24 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the superiority of P2B001 0.6/0.75 mg as compared to its individual components (PPX 0.6 mg and RAS 0.75 mg) in the change from Baseline to End of Week 12 Visit in the Total Unified Parkinson's Disease Rating Scale (UPDRS) Score (sum of Parts II + III). This scale is the standard measurement of Parkinson’s symptoms and is well recognised as reliable, accurate, and valid.

Protection of trial subjects:

The study and any amendments were reviewed and approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB). The study was monitored by an IDMC.
The study was 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.
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, were followed. The subjects were properly informed, given time to contemplate participation, and freely gave their consent by signing and dating the EC/IRB-approved informed consent form.
The consent form and any other documents relevant to the consent process were submitted to the IEC/IRB together with the protocol and approved prior to study start.
No rescue therapy was allowed during the treatment phase and for 2 weeks afterwards (until the safety follow-up visit), except in an emergency situation. If needed by the subject for adequate treatment of subject’s Parkinson's symptoms and according to the Investigator’s judgment, the study medication was discontinued and a rescue medication was administered.
A Data and Safety Monitoring Board (DSMB) periodically reviewed, in an unblinded fashion, safety data accumulated in the study. The data that the DSMB received included adverse events (AEs), vital signs,

and ECGs of subjects experiencing AEs.

Background therapy:

All concomitant medication that the subject took from the Screening visit, plus any changes in concomitant medication or new medications, were recorded.

Subjects were not permitted to receive concomitant therapy with any of the medications listed below for longer than 4 weeks or within the previous 1-3 months prior to baseline visit:

•Other investigational therapy (washout period 30 days prior to study entry, Baseline Visit).
•Previous monoamine oxidase (MAO)-B inhibitors
•Previous levodopa or dopamine agonists
•Previous anticholinergic drugs for PD
•Subjects were permitted to take peripheral anticholinergic drugs if they were stable on low dose for at least 4 weeks prior to study entry. Once enrolled into the study, use of new peripheral anticholinergic drugs was prohibited
•Non-selective MAO inhibitors
•Dopamine antagonists
•Ciprofloxacin or other CYP1A2 inhibitors that may affect RAS plasma concentrations
•Antitussive agent dextromethorphan: co-administration with RAS 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
•Marijuana or previous exposure to marijuana during the last 30 days

Care was taken to avoid or minimize use of sympathomimetic medications, including nasal, oral and ophthalmic decongestants and cold remedies due to possible hypertensive reactions.

Care was taken when study drugs were given with sedating medications (e.g., diphenhydramine, doxylamine succinate and other first-generation antihistamines) due to possible additive sedative effects with pramipexole.

Fifty-three subjects took antidepressant drugs concomitantly with the study medication. The subjects were closely followed up by site PI for signs of serotonin syndrome.

Evidence for comparator:

Pramipexole and rasagiline are both approved drugs and routinely used in standard therapy for the treatment of individuals with PD. They have different mechanisms and there is reason to believe that their combined activity will be better than each individual drug as monotherapy, and that lower doses of each could be used without losing the therapeutic effect, while avoiding the side effects associated with higher doses of both drugs when taken as monotherapy.

Actual start date of recruitment	19 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 103
Country: Number of subjects enrolled	United States: 380
Country: Number of subjects enrolled	Spain: 59
Country: Number of subjects enrolled	Canada: 2
Worldwide total number of subjects	544
EEA total number of subjects	162

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	268
From 65 to 84 years	276
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 70 sites in North America and Europe. A total of 544 subjects were recruited to allow for close to 525 eligible subjects. The safety analysis set (519 subjects) included treated subjects.

Pre-assignment

Screening details:

Eligibility was evaluated as per the inclusion/exclusion Criteria. Personal interviews included medical history, physical and neurological examinations, and evaluation for trial eligibility by clinical staff and an external eligibility monitoring committee (EMC).

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

To preserve blinding, capsules of P2B001 0.6/0.75 mg, PPX 0.6 mg, RAS 0.75 mg, and placebo were visually identical. Tablets of PramiER and their placebos were visually identical. Blinding was maintained throughout the study. All personnel involved in subject assessment, monitoring, analysis and data management were blinded to the subject assignment. Specific, independent, unblinded study personnel from the CRO were available to provide the DSMB with periodic reports.

Arms

Are arms mutually exclusive?	Yes
Arm title	P2B001

Arm description:

P2B001: a fixed-dose combination extended-release (ER) capsule containing 0.6 mg pramipexole and 0.75 mg rasagiline; plus PramiER placebo tablets.

Arm type	Experimental
Investigational medicinal product name	P2B001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were instructed to take 1 capsule by mouth with a glass of water (240 mL), with or without food, and at about the same time each day.

Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were instructed to take up to 3 PramiER placebo tablets (depending on dose 1.5-4.5 mg following titration phase) by mouth with a glass of water (240 mL), with or without food, and at about the same time each day.

Arm title	PPX 0.6

Arm description:

Pramipexole: ER capsule containing 0.6 mg pramipexole; plus PramiER placebo tablets.

Arm type	Active comparator

Investigational medicinal product name	Pramipexole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were instructed to take 1 capsule by mouth with a glass of water (240 mL), with or without food, and at about the same time each day.

Investigational medicinal product name	Placebo Tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were instructed to take up to 3 PramiER placebo tablets (depending on dose 1.5-4.5 mg following titration phase) by mouth with a glass of water (240 mL), with or without food, and at about the same time each day.

Arm title	RAS 0.75

Arm description:

Rasagiline: ER capsule containing 0.75 mg Rasagiline; plus PramiER placebo tablets.

Arm type	Active comparator
Investigational medicinal product name	Rasagiline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were instructed to take 1 capsule by mouth with a glass of water (240 mL), with or without food, and at about the same time each day.

Investigational medicinal product name	Placebo Tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were instructed to take up to 3 PramiER placebo tablets (depending on dose 1.5-4.5 mg following titration phase) by mouth with a glass of water (240 mL), with or without food, and at about the same time each day.

Arm title	PramiER

Arm description:

PramiER: currently marketed ER tablets; plus placebo capsules (matching the experimental arms).

Arm type	Active comparator
Investigational medicinal product name	PramiER
Investigational medicinal product code	
Other name	Pramipexole extended-release
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose of PramiER was 0.375 mg given once per day. Based on efficacy and tolerability, dosages were increased gradually, not more frequently than every 5 to 7 days, first to 0.75 mg per day and then by 0.75 and 1.5 mg increments up to a maximum recommended dose of 4.5 mg per day. E Subjects were instructed to take up to 3 PramiER placebo tablets (depending on dose 1.5-4.5 mg following titration phase) by mouth with a glass of water (240 mL), with or without food, and at about the same time each day.

Investigational medicinal product name	Placebo Capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were instructed to take placebo capsules by mouth with a glass of water (240 mL), with or without food, at about the same time every day.

Number of subjects in period 1	P2B001	PPX 0.6	RAS 0.75
Started	157	156	154
Completed	137	137	134
Not completed	20	19	20
Request of primary care physician or investigator	1	-	-
Unable to achieve minimum dose of PramiER (1.5 mg)	-	1	-
Adverse event, non-fatal	8	6	4
Other	1	2	1
Adverse event (prior to treatment)	-	-	1
Other reason (prior to first dose)	-	-	-
Additional non-protocol related therapy required	1	-	-
Withdrew consent prior to first dose	7	4	6
Erroneously randomised	-	4	-
Lack of efficacy	2	2	8

Number of subjects in period 1	PramiER
Started	77
Completed	67
Not completed	10
Request of primary care physician or investigator	-
Unable to achieve minimum dose of PramiER (1.5 mg)	-
Adverse event, non-fatal	5
Other	1
Adverse event (prior to treatment)	-
Other reason (prior to first dose)	1
Additional non-protocol related therapy required	-
Withdrew consent prior to first dose	2
Erroneously randomised	-
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	P2B001
Reporting group description:	
P2B001: a fixed-dose combination extended-release (ER) capsule containing 0.6 mg pramipexole and 0.75 mg rasagiline; plus PramiER placebo tablets.	
Reporting group title	PPX 0.6
Reporting group description:	
Pramipexole: ER capsule containing 0.6 mg pramipexole; plus PramiER placebo tablets.	
Reporting group title	RAS 0.75
Reporting group description:	
Rasagiline: ER capsule containing 0.75 mg Rasagiline; plus PramiER placebo tablets.	
Reporting group title	PramiER
Reporting group description:	
PramiER: currently marketed ER tablets; plus placebo capsules (matching the experimental arms).	

Reporting group values	P2B001	PPX 0.6	RAS 0.75
Number of subjects	157	156	154
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	63.9	64.9	65.1
standard deviation	± 9.4	± 8.4	± 9.5
Gender categorical			
Units: Subjects			
Female	51	52	48
Male	106	104	106
Baseline Total UPDRS Scores (Parts II+III)			
Unified Parkinson's Disease Rating Scale (UPDRS) defined as sum of Parts II + III (scores 0-160). This scale is the standard measurement of Parkinson’s symptoms and is well recognized as reliable, accurate, and valid.			
Units: UPDRS Scores (Parts II+III)			
arithmetic mean	30.7	31.3	31.3
standard deviation	± 9.9	± 11.0	± 10.2
Baseline Total UPDRS II ADL			
UPDRS II - a self-evaluation of the activities of daily life (ADLs) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food.			
Units: UPDRS II Score			
arithmetic mean	8.1	8.1	8.2
standard deviation	± 3.7	± 4.3	± 3.8
Baseline Total UPDRS III Motor			
UPDRS III - a clinician-scored monitored motor evaluation.			
Units: UPDRS III Score			
arithmetic mean	22.6	23.3	22.9
standard deviation	± 7.5	± 8.0	± 7.7
Baseline Total MMSE Score			

Mini mental state examination (MMSE) is a commonly used set of questions for screening cognitive function.			
Units: MMSE Score			
arithmetic mean	29.0	29.0	29.1
standard deviation	± 1.1	± 1.1	± 1.0
Baseline Total ESS Score			
The Epworth Sleepiness Scale (ESS) is a questionnaire to check a person’s sleepiness during the day.			
Units: ESS Score			
arithmetic mean	5.5	6.2	5.7
standard deviation	± 4.0	± 4.0	± 4.3

Reporting group values	PramiER	Total	
Number of subjects	77	544	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	63.9		
standard deviation	± 8.8	-	
Gender categorical			
Units: Subjects			
Female	24	175	
Male	53	369	
Baseline Total UPDRS Scores (Parts II+III)			
Unified Parkinson's Disease Rating Scale (UPDRS) defined as sum of Parts II + III (scores 0-160). This scale is the standard measurement of Parkinson’s symptoms and is well recognized as reliable, accurate, and valid.			
Units: UPDRS Scores (Parts II+III)			
arithmetic mean	28.8		
standard deviation	± 10.0	-	
Baseline Total UPDRS II ADL			
UPDRS II - a self-evaluation of the activities of daily life (ADLs) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food.			
Units: UPDRS II Score			
arithmetic mean	7.9		
standard deviation	± 4.5	-	
Baseline Total UPDRS III Motor			
UPDRS III - a clinician-scored monitored motor evaluation.			
Units: UPDRS III Score			
arithmetic mean	20.9		
standard deviation	± 6.9	-	
Baseline Total MMSE Score			
Mini mental state examination (MMSE) is a commonly used set of questions for screening cognitive function.			
Units: MMSE Score			
arithmetic mean	29.1		
standard deviation	± 1.1	-	
Baseline Total ESS Score			
The Epworth Sleepiness Scale (ESS) is a questionnaire to check a person’s sleepiness during the day.			
Units: ESS Score			
arithmetic mean	6.1		

standard deviation	± 4.1	-	

End points

End points reporting groups

Reporting group title	P2B001
Reporting group description:	
P2B001: a fixed-dose combination extended-release (ER) capsule containing 0.6 mg pramipexole and 0.75 mg rasagiline; plus PramiER placebo tablets.	
Reporting group title	PPX 0.6
Reporting group description:	
Pramipexole: ER capsule containing 0.6 mg pramipexole; plus PramiER placebo tablets.	
Reporting group title	RAS 0.75
Reporting group description:	
Rasagiline: ER capsule containing 0.75 mg Rasagiline; plus PramiER placebo tablets.	
Reporting group title	PramiER
Reporting group description:	
PramiER: currently marketed ER tablets; plus placebo capsules (matching the experimental arms).	

Primary: Total UPDRS score changes from baseline to Week 12

End point title	Total UPDRS score changes from baseline to Week 12
End point description:	
The primary efficacy endpoint for this study was the change from Baseline to Week 12 Visit in Total UPDRS score (defined as sum of Parts II + III, scores 0-160). The data is presented as a model adjusted LSM of the change from baseline in the mITT population.	
End point type	Primary
End point timeframe:	
From baseline to the end of Week 12.	

End point values	P2B001	PPX 0.6	RAS 0.75	PramiER
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	147	144	144	72
Units: UPDRS Score				
least squares mean (standard error)	-7.98 (± 0.60)	-5.32 (± 0.61)	-4.69 (± 0.61)	-8.35 (± 0.86)

Statistical analyses

Statistical analysis title	P2B001 vs PPX
Statistical analysis description:	
A mixed model repeated measures (MMRM) analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.	
Comparison groups	P2B001 v PPX 0.6

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-2.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.33
upper limit	-1
Variability estimate	Standard error of the mean
Dispersion value	0.85

Statistical analysis title	P2B001 vs RAS

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	RAS 0.75 v P2B001
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.96
upper limit	-1.63
Variability estimate	Standard error of the mean
Dispersion value	0.85

Statistical analysis title	P2B001 vs PramiER

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v PramiER

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.7197
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	2.42
Variability estimate	Standard error of the mean
Dispersion value	1.04

Notes:

[1] - Exploratory

Statistical analysis title	P2B001 vs PramiER - Non-inferiority

Statistical analysis description:

P2B001 was not statistically significantly different from a marketed dose of PramiER for the Total UPDRS (titrated to an optimal dose for each individual subject; 1.5-4.5 mg with
mean = 3.2 mg). A post-hoc non-inferiority analysis was conducted and showed that P2B001 is not inferior to PramiER using a 3-point threshold margin.

Comparison groups	P2B001 v PramiER
Number of subjects included in analysis	219
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.0052
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	2.18
Variability estimate	Standard error of the mean
Dispersion value	0.96

Secondary: Total ESS score changes from baseline to Week 12

End point title	Total ESS score changes from baseline to Week 12

End point description:

The first secondary endpoint was the change from baseline to end of Week 12 in total Epworth Sleepiness Scale (ESS) score. The data are presented as a model adjusted LSM of the change from baseline in the mITT population.

End point type	Secondary

End point timeframe:

From baseline to end of Week 12.

End point values	P2B001	PPX 0.6	RAS 0.75	PramiER
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	147	144	144	72
Units: ESS Score				
least squares mean (standard error)	-0.33 (± 0.25)	0.39 (± 0.25)	-0.81 (± 0.26)	2.33 (± 0.36)

Statistical analyses

Statistical analysis title	P2B001 vs PPX

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v PPX 0.6
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0399
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.41
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.35

Notes:

[2] - Exploratory

Statistical analysis title	P2B001 vs RAS

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v RAS 0.75

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.1756
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	1.17
Variability estimate	Standard error of the mean
Dispersion value	0.35

Notes:

[3] - Exploratory

Statistical analysis title	P2B001 vs PramiER

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v PramiER
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-2.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	-1.81
Variability estimate	Standard error of the mean
Dispersion value	0.43

Secondary: Total UPDRS III Motor changes from baseline to Week 12

End point title	Total UPDRS III Motor changes from baseline to Week 12

End point description:

The second secondary endpoint was the change from baseline to end of Week 12 in total UPDRS III Motor score. The data is presented as a model adjusted LSM of the change from baseline in the mITT population.

End point type	Secondary

End point timeframe:

From baseline to end of Week 12.

End point values	P2B001	PPX 0.6	RAS 0.75	PramiER
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	147	144	144	72
Units: UPDRS Score				
least squares mean (standard error)	-5.82 (± 0.47)	-4.30 (± 0.48)	-4.07 (± 0.48)	-6.38 (± 0.68)

Statistical analyses

Statistical analysis title	P2B001 vs PPX

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v PPX 0.6
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0231
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.84
upper limit	-0.21
Variability estimate	Standard error of the mean
Dispersion value	0.67

Notes:

[4] - Exploratory

Statistical analysis title	P2B001 vs RAS

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v RAS 0.75

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0092
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.06
upper limit	-0.43
Variability estimate	Standard error of the mean
Dispersion value	0.67

Notes:

[5] - Exploratory

Statistical analysis title	P2B001 vs PramiER

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v PramiER
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.5093
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	2.16
Variability estimate	Standard error of the mean
Dispersion value	0.82

Notes:

[6] - Exploratory

Secondary: Total UPDRS II ADL changes from baseline to Week 12

End point title	Total UPDRS II ADL changes from baseline to Week 12

End point description:

The third secondary endpoint was the change from baseline to end of Week 12 in total UPDRS II ADL score. The data is presented as a model adjusted LSM of the change from baseline in the mITT population.

End point type	Secondary

End point timeframe:

From baseline to end of Week 12.

End point values	P2B001	PPX 0.6	RAS 0.75	PramiER
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	147	144	144	72
Units: UPDRS Score				
least squares mean (standard error)	-2.14 (± 0.22)	-0.97 (± 0.22)	-0.62 (± 0.22)	-2.02 (± 0.31)

Statistical analyses

Statistical analysis title	P2B001 vs PPX

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v PPX 0.6
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.77
upper limit	-0.57
Variability estimate	Standard error of the mean
Dispersion value	0.31

Notes:

[7] - Exploratory

Statistical analysis title	P2B001 vs RAS

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v RAS 0.75

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.13
upper limit	-0.92
Variability estimate	Standard error of the mean
Dispersion value	0.31

Notes:

[8] - Exploratory

Statistical analysis title	P2B001 vs PramiER

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v PramiER
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.7367
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	0.61
Variability estimate	Standard error of the mean
Dispersion value	0.38

Notes:

[9] - Exploratory

Secondary: Change in ADL subscale score of PDQ39 from baseline to Week 12

End point title	Change in ADL subscale score of PDQ39 from baseline to Week 12

End point description:

The fourth secondary endpoint was the change from baseline to end of Week 12 in ADL subscale score of PDQ39. The data is presented as a model adjusted LSM of the change from baseline in the mITT population.

End point type	Secondary

End point timeframe:

From baseline to end of Week 12.

End point values	P2B001	PPX 0.6	RAS 0.75	PramiER
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	147	144	144	72
Units: PDQ39 score				
least squares mean (standard error)	-5.30 (± 0.89)	-3.40 (± 0.90)	-2.04 (± 0.92)	-3.12 (± 1.27)

Statistical analyses

Statistical analysis title	P2B001 vs PPX

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v PPX 0.6
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.1299
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.36
upper limit	0.56
Variability estimate	Standard error of the mean
Dispersion value	1.25

Notes:

[10] - Exploratory

Statistical analysis title	P2B001 vs RAS

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v RAS 0.75

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0099
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-3.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.73
upper limit	-0.79
Variability estimate	Standard error of the mean
Dispersion value	1.26

Notes:

[11] - Exploratory

Statistical analysis title	P2B001 vs PramiER

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v PramiER
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.1589
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.21
upper limit	0.85
Variability estimate	Standard error of the mean
Dispersion value	1.54

Notes:

[12] - Exploratory

Secondary: Total PDQ39 score changes from baseline to Week 12

End point title	Total PDQ39 score changes from baseline to Week 12

End point description:

The fifth secondary endpoint was the change from baseline to end of Week 12 in total PDQ39 score. The data is presented as a model adjusted LSM of the change from baseline in the mITT population.

End point type	Secondary

End point timeframe:

From baseline to end of Week 12.

End point values	P2B001	PPX 0.6	RAS 0.75	PramiER
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	147	144	144	72
Units: PDQ39 score				
least squares mean (standard error)	-2.58 (± 0.55)	-1.56 (± 0.55)	-1.33 (± 0.57)	-0.73 (± 0.78)

Statistical analyses

Statistical analysis title	P2B001 vs PPX

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v PPX 0.6
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.1789
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.53
upper limit	0.47
Variability estimate	Standard error of the mean
Dispersion value	0.76

Notes:

[13] - Exploratory

Statistical analysis title	P2B001 vs RAS

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v RAS 0.75

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.1047
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	0.26
Variability estimate	Standard error of the mean
Dispersion value	0.77

Notes:

[14] - Exploratory

Statistical analysis title	P2B001 vs PramiER

Statistical analysis description:

A MMRM analysis included fixed effects: categorical scheduled week by treatment interaction, CGR1 and baseline total UPDRS score. Unstructured covariance was used, and REML estimation method and degrees of freedom adjusted using the Kenward-Roger method. Data from all 3 scheduled changes from Baseline (derived) to post-Baseline visits (Weeks 5, 8 and 12) were used as response and differences between the treatments at Week 12 were estimated using contrasts.

Comparison groups	P2B001 v PramiER
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.0494
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.94

Notes:

[15] - Exploratory

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From baseline to end of Week 12.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	P2B001
Reporting group description: P2B001: a fixed-dose combination ER capsule containing 0.6 mg pramipexole and 0.75 mg rasagiline; plus PramiER placebo tablets.	
Reporting group title	PPX 0.6
Reporting group description: Pramipexole: ER capsule containing 0.6 mg pramipexole; plus PramiER placebo tablets.	
Reporting group title	RAS 0.75
Reporting group description: Rasagiline: ER capsule containing 0.75 mg Rasagiline; plus PramiER placebo tablets.	
Reporting group title	PramiER
Reporting group description: PramiER: currently marketed ER tablets; plus placebo capsules (matching the experimental arms).	

Serious adverse events	P2B001	PPX 0.6	RAS 0.75
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 150 (2.00%)	3 / 148 (2.03%)	2 / 147 (1.36%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 150 (0.67%)	0 / 148 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 150 (0.00%)	1 / 148 (0.68%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 150 (0.00%)	1 / 148 (0.68%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 150 (0.00%)	1 / 148 (0.68%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 148 (0.68%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 150 (0.67%)	0 / 148 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 150 (0.00%)	0 / 148 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			
subjects affected / exposed	0 / 150 (0.00%)	1 / 148 (0.68%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Corona virus infection			
subjects affected / exposed	0 / 150 (0.00%)	1 / 148 (0.68%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			

subjects affected / exposed	0 / 150 (0.00%)	0 / 148 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 150 (0.00%)	0 / 148 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 148 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	PramiER		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 74 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematochezia			

subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Corona virus infection			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Klebsiella sepsis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	P2B001	PPX 0.6	RAS 0.75
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 150 (52.00%)	86 / 148 (58.11%)	52 / 147 (35.37%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 150 (4.00%)	8 / 148 (5.41%)	5 / 147 (3.40%)
occurrences (all)	6	10	12
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	4 / 150 (2.67%)	5 / 148 (3.38%)	4 / 147 (2.72%)
occurrences (all)	4	6	4
Nervous system disorders			
Somnolence			
subjects affected / exposed	22 / 150 (14.67%)	27 / 148 (18.24%)	7 / 147 (4.76%)
occurrences (all)	25	32	7
Dizziness			
subjects affected / exposed	16 / 150 (10.67%)	14 / 148 (9.46%)	19 / 147 (12.93%)
occurrences (all)	18	15	21
Headache			
subjects affected / exposed	9 / 150 (6.00%)	14 / 148 (9.46%)	9 / 147 (6.12%)
occurrences (all)	14	15	12
Memory impairment			
subjects affected / exposed	0 / 150 (0.00%)	0 / 148 (0.00%)	1 / 147 (0.68%)
occurrences (all)	0	0	1
General disorders and administration			

site conditions Fatigue subjects affected / exposed occurrences (all)	23 / 150 (15.33%) 27	22 / 148 (14.86%) 25	2 / 147 (1.36%) 2
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	28 / 150 (18.67%) 33	24 / 148 (16.22%) 29	10 / 147 (6.80%) 10
Constipation subjects affected / exposed occurrences (all)	6 / 150 (4.00%) 6	11 / 148 (7.43%) 12	9 / 147 (6.12%) 9
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	13 / 150 (8.67%) 14	9 / 148 (6.08%) 9	4 / 147 (2.72%) 4
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	2 / 150 (1.33%) 2	10 / 148 (6.76%) 11	2 / 147 (1.36%) 2
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	3 / 150 (2.00%) 4	2 / 148 (1.35%) 2	2 / 147 (1.36%) 3

Non-serious adverse events	PramiER		
Total subjects affected by non-serious adverse events subjects affected / exposed	54 / 74 (72.97%)		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	1 / 74 (1.35%) 2		
Vascular disorders Orthostatic hypotension subjects affected / exposed occurrences (all)	9 / 74 (12.16%) 9		
Nervous system disorders Somnolence			

subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Memory impairment subjects affected / exposed occurrences (all)	23 / 74 (31.08%) 29 7 / 74 (9.46%) 7 5 / 74 (6.76%) 5 4 / 74 (5.41%) 5		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 13 / 74 (17.57%) 14		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	 17 / 74 (22.97%) 22 7 / 74 (9.46%) 7		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 7 / 74 (9.46%) 8		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	 4 / 74 (5.41%) 4		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 4 / 74 (5.41%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2018	• Revised text of inclusion criteria presented below: 3. Subject is male or female ≥35.0 years of age to ≤80.0 years of age at the time of enrollment. 5. Subject with disease duration less than 3 years since diagnosis. 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. *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 23 deleted • Change to Overall study design and plan description Text added: 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. • Change to Section 5.2 Revised text: 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).
16 July 2018	Continued from above: • Change to Section 7.5 Text added: o Early Study Termination(EST) o 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 o The reasons for withdrawal could include the following: o Subject withdrawal of consent and refusal to continue participation in study o Pregnancy o Adverse Event/Experience o Loss to follow-up/failure to return o Death • Change to Section 8.3.5 Revised text in section 8.3.5: 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. • Change to Section 10 Revised text in section 10: 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.

16 July 2018	Continued from above: • Change to Section 8.3.9 Revised text in section 8.3.9: 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). • Change to Section 9.2.3 Revised text in section 9.2.3: CSSRS-SLV • Change to Section 8.4.1 UPDRS Revised text: 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.
16 July 2018	Continued from above: • Change to Section 9.2.2 Revised text in section 9.2.2: 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. . Subjects that were 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.

16 July 2018	Continued from above: • Change to Section 9.2.3 Revised text in section 9.2.3: The time between visit 1 (screening), and visit 2 (baseline), will be no less than 24 hours and no more than 28 days (or 35 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 • Change to Section 12.2 Revised text in section 12.2: 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. • Change to Section 22.1 appendix I; schedule of activities Revised text below table: ** The maximal interval between the screening and baseline visits can be extended to 35 days; however, additional Sponsor approval will be required. • Change to Section 12.6 Revised text in section 12.6: 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.
16 July 2018	Continued from above: • Change to Section 12.7 Revised text in section 12.7: For study drug accountability, the subject will be requested to bring for visit 4-7, all empty, partially used or unused bottles from the box used during the previous month. • Change to Section 21 Investigator Agreements Deleted text: Place to add sponsor representative name and signature was deleted. • Change to Section 22.9 Appendix IX: UPDRS Deleted text: "half point scores are allowed for Part III questions)"

18 November 2020	• Change sponsor representative details on title page • Change to details on eligible subjects in each arm Revised text: 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 4.5 mg) using a randomization scheme of 2:2:2:1, respectively. • Change to Section 15.3 Revised text: 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. • Text added to Section 7.5 Early Discontinuation Subjects Text added on Early Treatment Termination (ETT): 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.
18 November 2020	Continued from above: • Text added to Section 7.5 Early Discontinuation Subjects Text added on Early Study Termination (ETT): 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 • Change to Section 9.2.2 Added text in section 9.2.2: 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. • Change to Section 9.2.3 Revised text in section 9.2.3: 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).

18 November 2020	Continued from above: • Change to Appendix I Added text below table of activities Appendix I: 35 – 90 days may be approved but a new collection of screening laboratory samples will be required to verify eligibility prior to baseline. • Change to Section 9.2.11 Revised text in section 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. • Change to definition of ITT analyses set in Section 15.4 Revised text: 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. • Change to definition of mITT analyses set in Section 15.4 Revised text: 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. • Change to Synopsis and Section 15.3 Added text: 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.
23 August 2021	Changes in the planned analysis prior to unblinding: The mITT analysis set in the original statistical analysis plan (SAP) (pre-SAP addendum) included only subjects who were randomised, took at least one dose of study drug, and had at least one post-baseline UPDRS (parts II + III) score at the planned scheduled visits. This definition excluded 13 subjects who terminated treatment or the study before the first post baseline scheduled visit at the end of Week 5, but completed a post-baseline UPDRS (parts II+III) measurement at an unscheduled visit. A change in the definition of mITT analysis set was submitted to the FDA prior to the unblinding of the study in an addendum to the SAP in which these subjects were included. The mITT analysis set according to the SAP addendum included subjects that were randomised, took at least one dose of study drug and had at least one post-baseline (UPDRS Parts II + III) score at the planned scheduled visits or at an unscheduled early termination visit. A sensitivity analysis to the principal analysis of the primary endpoint with the pre-SAP addendum analysis set was done to test the impact of this change.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported