RESEARCH ARTICLE

A Randomized Phase 3 Study Comparing P2B001 to its Components (Low-Dose Extended-Release Rasagiline and Pramipexole) and to Optimized Doses of Marketed Extended-Release Pramipexole in Early Parkinson's Disease

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ABSTRACT: Background: There remains uncertainty as to the optimal way to initiate therapy for Parkinson's disease (PD) to maximize benefit and minimize adversity.

Objectives: The objective was to determine if P2B001 (a fixed, low-dose, extended-release [ER] combination of pramipexole 0.6 mg and rasagiline 0.75 mg) is superior to each of its components and compare its safety and efficacy to optimized treatment with marketed doses of pramipexole-ER.

Methods: This was a 12-week, double-blind study (NCT03329508). Total of 544 untreated patients with PD were randomized (2:2:2:1) to treatment with P2B001, its individual components (pramipexole-ER 0.6 mg or rasagiline-ER 0.75 mg), or commercial doses of pramipexole-ER titrated to optimal dose (1.5–4.5 mg). The primary endpoint was change from baseline to week 12 in Unified Parkinson's Disease Rating Scale (UPDRS) parts II and III. The key secondary endpoint was the change from baseline in the Epworth Sleepiness Scale (ESS) for P2B001 versus the titrated dose of pramipexole-ER.

Results: P2B001 provided superior efficacy compared to each of its components; mean (95% CI) treatment differences in UPDRS II + III scores were −2.66 (95% CI, −4.33 to −1.00) versus pramipexole-ER 0.6 mg ($P = 0.0018$) and − 3.30 (95% CI, −4.96 to −1.63) versus rasagiline-ER 0.75 mg ($P < 0.0001$). P2B001 had comparable efficacy with the titrated dose of pramipexole-ER (mean, 3.2 mg), but significantly less worsening in daytime-sleepiness (ESS treatment difference: −2.66 [95% CI, −3.50 to −1.81]; $P < 0.0001$). P2B001 was well-tolerated with fewer sleep-related and dopaminergic adverse events than titrated doses of pramipexole-ER including somnolence, orthostatic hypotension, and neuropsychiatric side effects.

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Conclusions: P2B001 had superior efficacy to its individual components and was comparable with commercially used doses of pramipexole-ER with less worsening of sleepiness and fewer dopaminergic adverse events. These findings support considering once-daily P2B001 as initial therapy for patients with early PD. © 2023 International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; P2B001; pramipexole; rasagiline

Introduction

Parkinson's disease (PD) is the second commonest neurodegenerative disease, affecting an estimated 5 to 10 million persons globally.[1] Although there are effective treatments for the motor features in the early stages of the disease, there remains debate as to the optimal way to initiate therapy to obtain satisfactory benefit with minimal adversity.

Levodopa (L-dopa) is the most effective anti-parkinsonian therapy,[2] but chronic treatment is associated with the development of motor complications in as many as 20% of patients within 9 months of treatment,[3] 75% within 3 years,[4] and virtually all patients over the course of the illness.[5] These complications are an important source of disability and are the most common reason for surgical therapies in patients with PD. Dopamine agonists have been used as initial therapy because they have a reduced risk of motor complications.[6,7] However, they are less effective than L-dopa with a less favorable side effect profile that includes daytime somnolence with sudden onset sleep episodes that can occur without warning in dangerous situations, such as while driving, and impulse control disorders such as compulsive gambling and hypersexuality.[8,9] Additionally, dopamine agonists require titration, which can take several weeks to achieve an effective dose. MAO-B inhibitors block the oxidative metabolism of dopamine to increase synaptic dopamine levels and are another consideration for initial therapy of PD.[10] They have a good safety profile and do not cause motor complications, but do not have comparable efficacy with L-dopa or dopamine agonists. The American Academy of Neurology recently proposed guidelines for initiating therapy for PD patients[11] and recommended starting with L-dopa, recognizing the limitations of the drug particularly with respect to motor complications. Therefore, there is currently no ideal approach for initiating treatment for PD patients that provides satisfactory benefit with minimal short and long-term safety risks.

P2B001 is a fixed combination of low dose and extended-release formulations of pramipexole-extended-release (PPX-ER) (0.6 mg) and rasagiline-ER (RAS-ER) (0.75 mg), two approved drugs routinely used in the treatment of PD.[12] The doses chosen are lower than those currently approved as monotherapy for PD, and rasagiline is administered as a novel extended-release formulation. Studies in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned rodents have demonstrated that the low-dose combination had synergistic pharmacologic and behavioral effects that were enhanced when the drugs were administered in an extended-release formulation (data on file at Pharma Two B). A randomized, double-blind placebo-controlled-dose ranging trial in PD patients demonstrated that each of two doses of P2B001 (PPX-ER/RAS-ER: 0.6 mg/0.75 mg and 0.3 mg/0.75 mg) provided significant benefit in comparison with placebo using total Unified Parkinson's Disease Rating Scale (UPDRS) score (sum of parts I–III) as the primary endpoint (difference of 4.67 ± 1.28 and 3.84 ± 1.25 points, respectively; $P = 0.0001$ and $P = 0.0002$).[13] Both P2B001 doses were well-tolerated and had good safety profiles. Regulatory requirements necessitate a demonstration that a combination product is superior to each of its components, and that each component contributes to the benefit of the combination product. The present study was designed to determine if P2B001 has superior efficacy to each of its components, and additionally, compared the safety and efficacy of P2B001 to treatment with standard doses of pramipexole-ER (PramiER) titrated to optimal benefit.

Methods

Study Conduct

This was an international, multicenter, randomized, double-blind, parallel-group study in patients with early untreated PD comparing once-daily P2B001 (PPX-ER/RAS-ER: 0.6 mg/0.75 mg) to its individual components and to marketed doses of standard PramiER titrated to optimal benefit. The study was conducted between January 2018 and October 2021. All patients provided institutional review board-approved informed consent before participation. The study was registered at ClinicalTrials.gov (NCT03329508) and was executed in accordance with the declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines.

Study Population

Patients were men or women of all races, ages 35 to 80 years with a diagnosis of PD consistent with United Kingdom Brain Bank Criteria, <3 years duration from time of diagnosis, Hoehn and Yahr stage <3, and not receiving anti-parkinsonian therapy. Exclusion criteria included atypical or secondary parkinsonism,

use of a neuroleptic agent in the preceding 3 months, and clinically significant medical, surgical, psychiatric, or laboratory abnormalities. Patients were approved by an Eligibility Monitoring Committee before randomization to ensure accuracy of diagnosis and suitability for the trial.

Randomization and Masking

Eligible patients were randomized using a computer generated scheme in a ratio of 2:2:2:1 to once-daily treatment with P2B001, PPX-ER 0.6 mg, RAS-ER 0.75 mg, or commercially available PramiER titrated to optimal dose (1.5–4.5 mg). The randomization list comprised permuted blocks stratified by region. To maintain blinding, patients were treated using a double-dummy design where each patient took one capsule (containing P2B001, PPX-ER 0.6 mg, RAS-ER 0.75 mg, or matching placebo) and 1 to 3 tablets (containing 1.5 mg of standard PramiER or matching placebo).

Procedures

The study consisted of a screening phase, a 6-week titration phase during which PramiER doses could be adjusted, a 6-week maintenance phase during which doses could not be further changed, and a 4 to 8 days down-titration phase with safety follow-up at week 14. The capsule (P2B001, separate P2B001 components, or placebo) was taken once-daily during the titration and maintenance phases of study. During the first 3 weeks of the titration phase, the commercially available PramiER or placebo tablet was up titrated in weekly increments to a daily dose of 1.5 mg. During the next 3 weeks the dose could be further titrated to a maximal dose of 4.5 mg or reduced to a minimum of 1.5 mg based on satisfactory efficacy and tolerability. All treatment was held constant during the maintenance phase.

Outcomes

Patients were assessed at baseline and at weeks 5, 8, and 12. Evaluations performed at each visit included the UPDRS,[14] Epworth Sleepiness Scale (ESS),[15] Clinical Global Impression of Improvement (CGI-I),[16] Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS),[17] and the Columbia Suicide Severity Rating Scale (C-SSRS).[18] The Parkinson's disease questionnaire (PDQ-39) was performed at baseline and week 12.[19] Treatment-emergent adverse events (TEAEs) and vital signs were recorded at each visit. TEAEs of special interest included dopaminergic, gastrointestinal, or sleep-related adverse events (AEs) as well as orthostatic hypotension, day-time sleepiness, depression, and impulse control or obsessive-compulsive disorders. Physical and neurological examinations, standard laboratory tests, and electrocardiogram (ECG) recordings were performed at baseline and final visits.

Statistical Analysis

The intention to treat population (ITT) included all randomized patients who received a dose of study medication and was used for safety analyses. The modified intention to treat population (mITT) included all randomized patients who received a dose of study medication and had a post randomization evaluation of the primary endpoint and was used for efficacy analyses.

The primary endpoint was change from baseline to Week 12 in total UPDRS score (defined as the sum of parts II and III) comparing P2B001 to its individual components (PPX-ER and RAS-ER). The key (first) secondary endpoint was the change from baseline to week 12 in the ESS score comparing P2B001 to the optimized dosage of PramiER. Other secondary endpoints in prespecified hierarchical order were the change from baseline to week 12 comparing P2B001 to its components in UPDRS part III (motor) score, UPDRS part II (activities of daily living [ADL]) score, PDQ-39 ADL subscale score, and PDQ-39 total score. Exploratory endpoints included responder analysis examining patients who experienced a change of ≥4 UPDRS points in total score, and a shift analysis comparing percent of patients who converted from an ESS score ≤10 at baseline to >10 at week 12.

The primary endpoint was analyzed in the mITT population, based on a multiply imputed dataset. For patients who used rescue therapy during the study, the observations collected post rescue therapy initiation was not used in the analysis. For these observations, data were imputed using the assumption of missing not at random (MNAR), with the rasagiline (RAS 0.75) group as reference in the copy-reference imputation. For the remaining missing data, including patients who discontinued the study, data were imputed using the assumption of missing at random. The imputed datasets were analyzed using the mixed model for repeated measures (MMRM). The model used the unstructured covariance matrix, the restricted maximum likelihood estimation method, and degrees of freedom using the Kenward-Roger method. Changes from baseline to weeks 5, 8, and 12 were used as the response and categorical study week, treatment group, week by treatment interaction, and geographical region, and baseline total UPDRS score were used as independent variables in the MMRM. Differences between the treatments groups at week 12 were estimated using contrasts. The primary endpoint was considered met only if both comparisons versus components favored P2B001 at a 2-tailed α level of 5%.

Sensitivity analyses included MMRM analyses of the completer and per protocol populations, MMRM

analysis based on multiple imputations assuming MNAR for all missing data, and a tipping point analysis. Secondary endpoints were evaluated using the same methodology as the primary endpoint. The overall significance level for this study was 5% using 2-tailed tests using the hierarchical gate keeping method to control the overall type I error rate. Safety analyses were descriptive and included an evaluation of the temporal profile of dopaminergic and sleep-related TEAEs.

A sample size of 150 patients per group provided >80% power to detect an improvement of 3.0 and 2.25 ± 6 points in total UPDRS score comparing P2B001 to RAS-ER 0.75 mg or PPX-ER 0.6 mg, respectively, assuming 5% α and 10% drop out. This sample size also provided >90% power to detect an effect size of 1.5 ± 3 points in ESS score compared to 75 patients in the standard PramiER arm. To examine whether the variance estimate used in power calculations for the primary endpoint was adequate, a blinded assessment of the variance of the change from baseline to week 12/treatment termination in the primary endpoint[20] was performed after one third of the subjects completed the study treatment period.

Results

Patient Disposition and Baseline Characteristics

A total of 676 patients were screened and 544 were enrolled and randomized into the study. Twenty-five of the patients who were randomized did not start treatment with their allocated study medication and did not have post-randomization evaluations (many related to the coronavirus disease [COVID]) and were, therefore, not included in the mITT population. A total of 475 of the remaining 519 (87.3%) patients completed the study. Reasons for early termination are provided in Figure 1. Patient baseline demographics are presented in Table 1; there were no significant differences between treatment groups. Patients randomized to receive standard PramiER were individually titrated in a double-blind fashion to a mean dose of 3.2 ± 1.3 mg/day.

Efficacy Results

Efficacy results are provided in Table 2. The change from baseline in total UPDRS (primary endpoint) showed that P2B001 was significantly superior to each of its individual components. Least squares mean (LSM) (standard error) treatment difference between P2B001 and PPX-ER 0.6 mg was −2.66 ± 0.85 points ($P = 0.0018$), and between P2B001 and RAS-ER 0.75 mg was −3.30 ± 0.85 points ($P = 0.0001$). Change from baseline at each visit is presented in Figure 2. The change from baseline to week 12 in total UPDRS score between P2B001 and optimized doses of PramiER (mean, 3.2 mg/day) was not significantly different (−8.35 ± 0.86 vs. 7.98 ± 0.60; $P = 0.7197$). A post hoc non-inferiority analysis demonstrated that P2B001 was not inferior to optimized doses of PramiER. A responder analysis examining patients who experienced a change of ≥4 UPDRS points in total UPDRS score showed significantly more responders in the P2B001 treatment group than in the PPX-ER 0.6 mg and RAS-ER 0.75 mg groups (74.1% vs. 58.8% and 54.5%; $P = 0.0098$ and $P = 0.0012$, respectively); percent responders with marketed doses of PramiER group (76.6%) was similar to the P2B001 group.

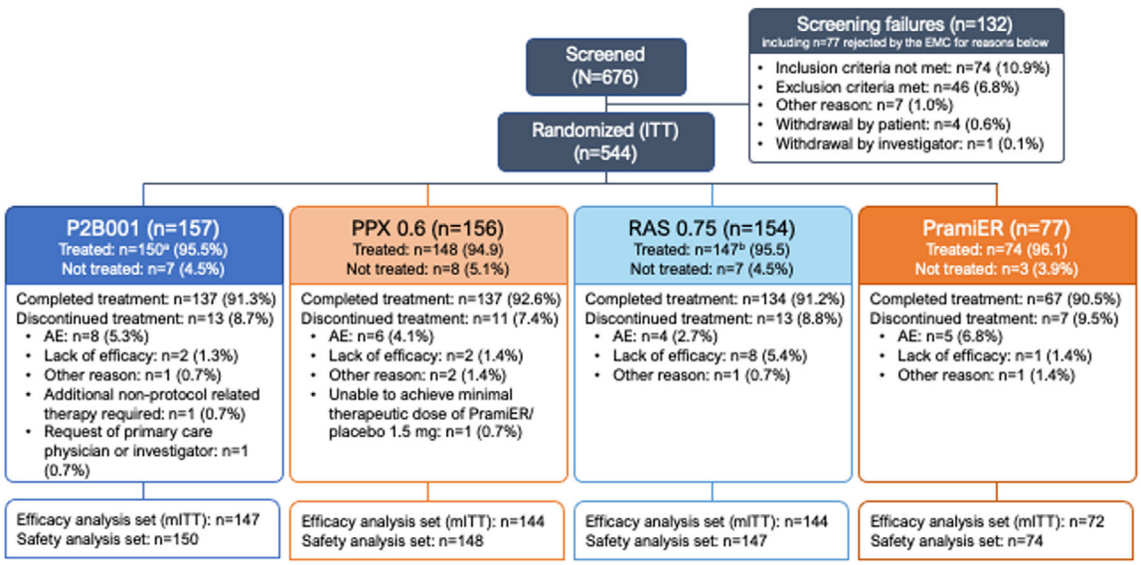

FIG. 1. Patient disposition. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 *Demographics and baseline disease characteristics (ITT set)*

	P2B001 (n = 157)	PPX-ER 0.6 mg (n = 156)	RAS-ER 0.75 mg (n = 154)	PramiER (n = 77)
Age (years); mean ± SD	63.9 ± 9.4	64.9 ± 8.4	65.1 ± 9.5	63.9 ± 8.8
Male sex, n (%)	106 (67.5)	104 (66.7)	106 (68.8)	53 (68.8)
Time since diagnosis, months; mean ± SD	5.1 ± 7.6	4.4 ± 5.8)	5.8 ± 7.9	5.8 ± 8.2
Hoehn and Yahr stage 2/2.5, n (%)	120 (76.4)	123 (78.8)	118 (76.6)	59 (76.6)
MMSE score; mean ± SD	29.0 ± 1.1	29.0 ± 1.1	29.1 ± 1.0	29.1 ± 1.1
UPDRS total; mean ± SD	30.7 ± 9.9	31.3 ± 11.0	31.3 ± 10.2	28.8 ± 10.0
UPDRS motor (part III) score; mean ± SD	22.6 ± 7.5	23.3 ± 8.0	22.9 ± 7.7	20.9 ± 6.9
UPDRS ADL (part II) score; mean ± SD	8.1 ± 3.7	8.1 ± 4.3	8.2 ± 3.8	7.9 ± 4.5
ESS score; mean ± SD	5.5 ± 4.0	6.2 ± 4.0	5.7 ± 4.3	6.1 ± 4.1
PDQ-39 score; mean ± SD	13.4 ± 9.9	13.4 ± 9.2	15.1 ± 11.0	13.1 ± 10.5

Abbreviations: ITT, intention to treat population; P2B001, a fixed, low-dose, extended-release combination of pramipexole 0.6 mg and rasagiline 0.75 mg; PPX-ER, pramipexole-extended-release; RAS-ER, rasagiline-extended-release; PramiER, pramipexole-extended-release titrated to optimal dose; SD, standard deviation; MMSE, mini mental state examination, UPDRS, Unified Parkinson's Disease Rating Scale, ADL, activities of daily living, ESS, Epworth Sleepiness Scale, PDQ-39, Parkinson's disease questionnaire 39-items.

Analysis of the key secondary endpoint (change from baseline to week 12 in the ESS score), demonstrated that optimized doses of PramiER (mean dose, 3.2 mg) caused significant worsening in ESS, whereas there was no worsening with P2B001 treatment (Table 2). LSM difference between groups was −2.66 ± 0.43 ($P < 0.0001$). The proportion of patients with a shift in ESS score from ≤10 at baseline to >10 post-baseline was significantly higher in the PramiER versus the P2B001 group (35.7% vs. 8.5%; $P < 0.0001$). P2B001 was also significantly superior to both components (PPX-ER and RAS-ER) with respect to the 2nd secondary endpoint (UPDRS motor score; $P = 0.023$ and $P = 0.0092$, respectively) and the 3rd secondary outcome measure (UPDRS ADL scores; $P = 0.0001$ and $P < 0.0001$, respectively) (Supplementary Fig. S1). P2B001 was not superior to its components on PDQ-39 ADL scores ($P = 0.1589$) (4th secondary endpoint), therefore, halting the hierarchical gatekeeping procedure. P2B001 was nominally superior to both of its components for CGI-I. There were no significant differences between P2B001 and PramiER with respect to the 2nd and 3rd secondary outcome measures.

During the study, because of COVID-related staffing issues at the contract distribution facility, some study kits were shipped to the enrolling centers with the treatment allocation erroneously noted on the packing list. A formal audit was performed, showing that no study patient or investigator was aware of this error, and all remained blind as to treatment allocation. Further, a sensitivity analysis excluding the affected patients, showed no difference in the effect size or P value in comparison with the primary analysis (P2B001 vs. PPX-ER 0.6 mg) (LSM −2.99 ± 0.89; $P = 0.0009$) and versus RAS-ER 0.75 mg (LSM –3.33 ± 0.88; $P = 0.0002$).

Safety and Tolerability

A total of 74.7% of patients experienced ≥1 TEAE with P2B001 versus 73.6% with PPX-ER 0.6 mg, 59.2% with RAS-ER 0.75 mg, and 86.5% with optimized doses of standard PramiER. AEs occurring in >2% of patients in any group are provided in Table 3. There were no deaths during the study. A total of 14 serious AEs were reported in eight patients (P2B001: cerebrovascular accident, hypokalemia [three reports in one patient], pneumothorax; PPX-ER: anemia, COVID-19, GI hemorrhage, hematochezia, muscle hemorrhage, prostatitis; RAS-ER: acute kidney injury, Klebsiella, sepsis; PramiER: none). All were categorized as "unrelated to study drug" by treating investigators. Patient discontinuations because of TEAEs are listed in Figure 1 and were highest for commercially used doses of PramiER (6.8%). There was a lower frequency of dopaminergic-related TEAEs with P2B001 compared with titrated doses of standard PramiER (44.7% vs. 66.2%). AEs of special interest occurred with a lower frequency in P2B001-treated patients than optimized PramiER; somnolence (14.7% vs. 31.1%), orthostatic hypotension (2.7% vs. 12.7%), constipation (4.0% vs. 9.5%), memory impairment (0 vs. 5.4%), and hallucinations (2.0% vs. 4.1%). The temporal profile of dopaminergic events, and specifically daytime sleepiness, illustrates that the increased frequency of these AEs persisted throughout the study with standard PramiER treatment (Supplementary Fig. S2). There were no

TABLE 2 *Primary, secondary, and exploratory efficacy results (mITT set)*

	P2B001 (n = 147)	PPX-ER 0.6 mg (n = 144)	RAS-ER 0.75 mg (n = 144)	PramiER (n = 72) (mean dose, 3.2 mg)
UPDRS total score at week 12		(Primary endpoint)	(Primary endpoint)	
LS mean ± SE change from baseline	−7.98 ± 0.60	−5.32 ± 0.61	−4.69 ± 0.61	−8.35 ± 0.86
Mean [95% CI] treatment difference		−2.66 [−4.33 to −1.00]	−3.30 [−4.96 to −1.63]	0.37 [−1.67 to 2.42]
P value for comparison with P2B 00		*P* = 0.0018	*P* = 0.0001	*P* = 0.7197★
ESS score at week 12				
LS mean ± SE change from baseline	−0.33 ± 0.25	0.39 ± 0.25	−0.81 ± 0.26	2.33 ± 0.36
Mean [95% CI] treatment difference		−0.72 [−1.41 to −0.03]	0.48 [−0.21 to 1.17]	−2.66 [−3.50 to −1.81]
P value for comparison		*P* = 0.0399★	*P* = 0.1756★	*P* < 0.0001
UPDRS motor score at week 12				
LS mean ± SE change from baseline	−5.82 ± 0.47	−4.30 ± 0.48	−4.07 ± 0.48	−6.36 ± 0.68
Mean [95% CI] treatment difference		−1.52 [−2.84 to −0.21]	−1.75 [−3.06 to −0.43]	0.54 [−1.07 to 2.16]
P value for comparison		*P* = 0.023	*P* = 0.0092	*P* = 0.5093★
UPDRS ADL score at Week 12				
LS mean ± SE change from baseline	−2.14 ± 0.22	−0.97 ± 0.22	−0.62 ± 0.22	−2.02 ± 0.31
Mean [95% CI] treatment difference		−1.17 [−1.77 to −0.57]	−1.52 [−2.13 to −0.92]	−0.13 [−0.87 to 0.61]
P value for comparison		*P* = 0.0001	*P* < 0.0001	*P* = 0.7367★
PDQ-39 ADL score at week 12				
LS mean ± SE change from baseline	−5.30 ± 0.89	−3.40 ± 0.90	−2.04 ± 0.92	−3.12 ± 1.27
Mean [95% CI] treatment difference		−1.90 [−4.36 to 0.56]	−3.26 [−5.73 to −0.79]	−2.18 [−5.21 to 0.85]
P value for comparison		*P*= 0.1299	*P*= 0.0099	*P* = 0.1589★
PDQ-39 total score at week 12				
LS mean ± SE change from baseline	−2.58 ± 0.55	−1.56 ± 0.55	−1.33 ± 0.57	−0.73 ± 0.78
Mean [95% CI] treatment difference		−1.03 [−2.53 to 0.47]	−1.26 [−2.78 to 0.26]	−1.85 [−3.70 to 0.00]
P value for comparison		*P* = 0.1789★★	*P* = 0.1047★★	*P* = 0.0494★
CGI-I responder at week 12				
Responder rate ± SE %	37.1% ± 5.8%	21.8% ± 4.6%	21.0% ± 4.6%	38.5% ± 8.2%
Odds ratio [95% CI] P2B001 vs. comparator	37.1% ± 5.8%	2.11 [1.04 to 4.30]	2.22 [1.08 to 4.58]	0.94 [0.41 to 2.17]
P value		*P* = 0.0392★	*P* = 0.0306★	*P* = 0.8877★
UPDRS responder at week 12				
Responder rate ± SE %	74.1% ± 3.9%	58.8% ± 4.5%	54.5% ± 4.5%	76.6% ± 5.3%
Odds ratio [95% CI] P2B001 vs. comparator		2.01 [1.18 to 3.41]	2.39 [1.41 to 4.05]	0.87 [0.44 to 1.75]
P value		*P* = 0.0098★	*P* = 0.001★	*P* = 0.70★

CGI responders were defined as those patients rated by site neurologist as "much improved" or "very much improved." UPDRS responders were defined as those patients showing ≥4-point improvement in UPDRS Total (part II and III) scores.

Abbreviations: mITT, modified intention to treat population; P2B001, a fixed, low-dose, extended-release combination of pramipexole 0.6 mg and rasagiline 0.75 mg; PPX-ER, pramipexole-extended-release; RAS-ER, rasagiline-extended-release; PramiER, pramipexole-extended-release titrated to optimal dose; UPDRS, Unified Parkinson's Disease Rating Scale; LS, least squares; SE, standard error; CI, confidence interval; ESS, Epworth Sleepiness Scale; ADL, activities of daily living; PDQ-39, Parkinson's disease questionnaire 39-items; CGI-I, Clinical Global Impression of Improvement.

★Exploratory *P* value.

★★Nominal *P* value following hierarchical gateway procedure.

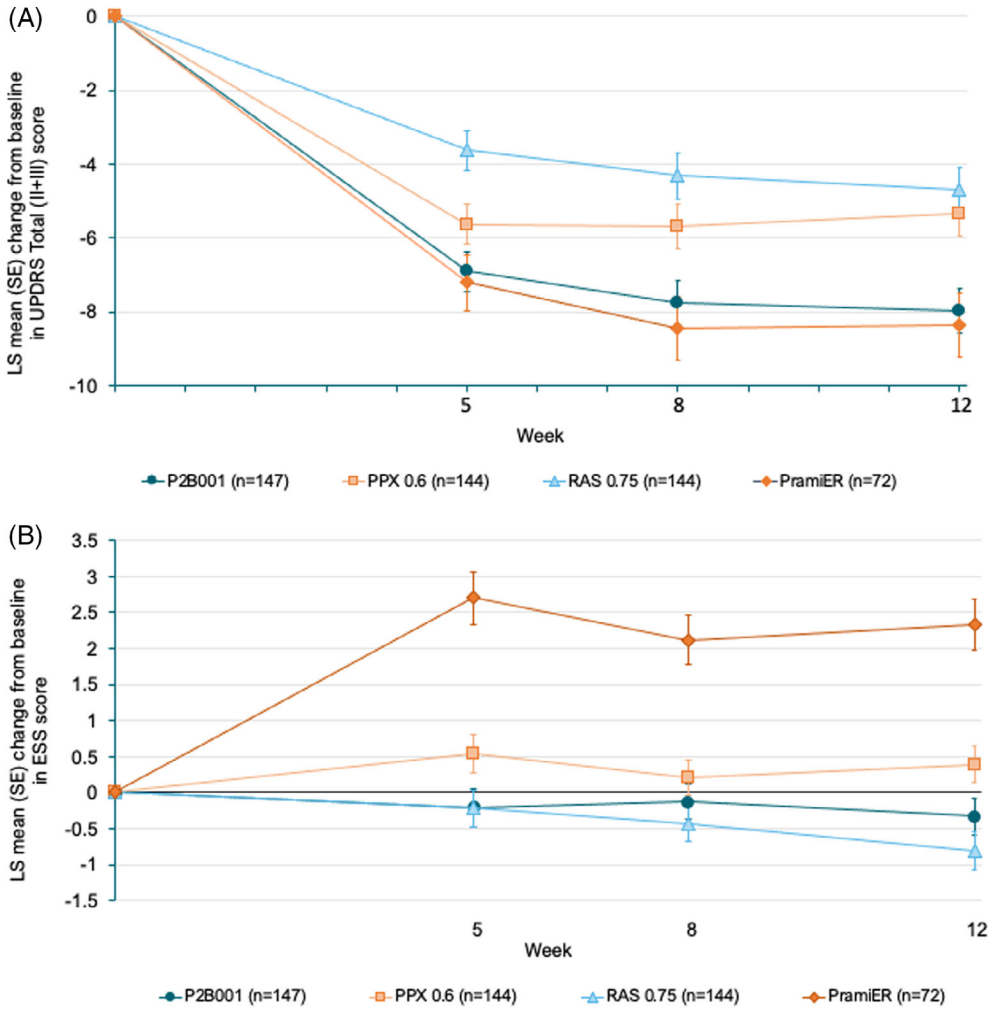

FIG. 2. Mean (standard error) reduction in (**A**) UPDRS total scores (**B**) total ESS scores. Model adjusted least square means (±standard error) of change from baseline over time (modified intention to treat population). ESS, Epworth Sleepiness Scale, UPDRS, Unified Parkinson's Disease Rating Scale. [Color figure can be viewed at wileyonlinelibrary.com]

clinically significant changes in laboratory tests, ECG parameters, or physical/neurological examination for any treatment group nor was there any significant change in QUIP-RS or CSRS score, or indication of any patient developing a clinically significant impulse control disorder or suicidality.

Discussion

We demonstrate that P2B001, a capsule containing a combination of low-dose extended-release formulations of pramipexole and rasagiline, is superior to each of its components with respect to the primary endpoint (change from baseline to final visit in total UPDRS score; $P = 0.0018$ and $P = 0.0001$, respectively). Superiority of P2B001 over each of its PPX-ER and RAS-ER components was also observed for the motor subscale of the UPDRS (2nd secondary outcome measure; $P = 0.023$ and $P = 0.0092$, respectively) and the ADL subscale of the UPDRS (3rd secondary outcome measure; $P = 0.0001$ for both). A responder analysis showed significantly more patients on P2B001 improved by 4 UPDRS points in comparison to either component. This cutoff point is slightly below the range for accepted clinically meaningful differences in UPDRS score (>4.5 points) suggested by Shulman et al[21]; a post hoc analysis showed similar results using a cutoff of 4.5 points. A previous double-blind placebo-controlled study in patients with early PD demonstrated that two different doses of P2B001 were each significantly better than placebo ($P = 0.0027$ and $P = 0.0004$ for 0.6/0.75 and 0.3/0.75 mg doses, respectively).[13] The present study demonstrates that each component contributes to the beneficial effect of the P2B001 combination capsule.

It is noteworthy that in comparison with commercially available doses of PramiER titrated to optimal benefit (mean dose of 3.2 mg), P2B001 showed comparable efficacy with respect to total and both UPDRS motor and ADL subscales (Table 3), but had significantly less

TABLE 3 *Summary of treatment-emergent adverse events occurring in ≥2% of any group*

No. (%)	P2B001 (n = 150)	PPX-ER 0.6 mg (n = 148)	RAS-ER 0.75 mg (n = 147)	PramiER (mean dosage 3.2 mg) (n = 74)
At least one TEAE	112 (74.7)	109 (73.6)	87 (59.2)	64 (86.5)
At least one dopaminergic TEAE	67 (44.7)	72 (48.6)	50 (34.0)	49 (66.2)
TEAEs in >2% in any group				
Nausea	28 (18.7)	24 (16.2)	10 (6.8)	17 (23.0)
Fatigue	23 (15.3)	22 (14.9)	2 (1.4)	13 (17.6)
Somnolence	22 (14.7)	27 (18.2)	7 (4.8)	23 (31.0)
Dizziness	16 (10.7)	14 (9.5)	19 (12.9)	7 (9.5)
Insomnia	13 (8.7)	9 (6.1)	4 (2.7)	7 (9.5)
Headache	9 (6.0)	14 (9.5)	9 (6.1)	5 (6.8)
Fall	6 (4.0)	8 (5.4)	5 (3.4)	1 (1.4)
Constipation	6 (4.0)	11 (7.4)	9 (6.1)	7 (9.5)
Anxiety	5 (3.3)	1 (0.7)	2 (1.4)	3 (4.1)
Nasopharyngitis	5 (3.3)	7 (4.7)	6 (4.1)	2 (2.7)
Arthralgia	4 (2.7)	3 (2.0)	3 (2.0)	1 (1.4)
Dyspepsia	4 (2.7)	4 (2.7)	3 (2.0)	1 (1.4)
Back pain	4 (2.7)	2 (1.4)	3 (2.0)	2 (2.7)
Orthostatic hypotension	4 (2.7)	5 (3.4)	4 (2.7)	9 (12.2)
Hypotension	4 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)
Feeling abnormal	3 (2.0)	2 (1.4)	1 (0.7)	2 (2.7)
Vomiting	3 (2.0)	6 (4.1)	1 (0.7)	3 (4.1)
Hallucination	3 (2.0)	0 (0.0)	1 (0.7)	3 (4.1)
Decreased appetite	3 (2.0)	2 (1.4)	2 (1.4)	4 (5.4)
Pain in extremity	2 (1.3)	10 (6.8)	2 (1.4)	4 (5.4)
Cough	2 (1.3)	1 (0.7)	4 (2.7)	1 (1.4)
Diarrhea	2 (1.3)	5 (3.4)	4 (2.7)	2 (2.7)
Sleep disorder	2 (1.3)	3 (2.0)	4 (2.7)	0 (0.0)
Asthenia	1 (0.7)	1 (0.7)	3 (2.0)	2 (2.7)
Disturbance in attention	1 (0.7)	1 (0.7)	0 (0.0)	2 (2.7)
Hallucination, visual	1 (0.7)	2 (1.4)	0 (0.0)	2 (2.7)
Edema peripheral	1 (0.7)	5 (3.4)	0 (0.0)	3 (4.1)
Gait disturbance	1 (0.7)	2 (1.4)	1 (0.7)	2 (2.7)
Memory impairment	1 (0.7)	0 (0.0)	1 (0.7)	4 (5.4)
Confusional state	1 (0.7)	2 (1.4)	2 (1.4)	2 (2.7)
Aphasia	1 (0.7)	0 (0.0)	0 (0.0)	2 (2.7)

Dopaminergic events included orthostatic hypotension, impulse control disorders, constipation, dizziness, hallucination, nausea, edema, somnolence, and sleep-disorders.
Abbreviations: P2B001, a fixed, low-dose, extended-release combination of pramipexole 0.6 mg and rasagiline 0.75 mg; PPX-ER, pramipexole-extended-release; RAS-ER, rasagiline-extended-release; PramiER, pramipexole-extended-release titrated to optimal dose; TEAE, treatment emergent adverse event.

worsening in ESS ($P < 0.0001$) and had fewer reported complaints of somnolence and dopaminergic side effects including nausea, orthostatic hypotension, constipation, and hallucinations. A mean dose of 3.2 ± 1.3 mg/day of PramiER is approximately the same as the average dose used in treating PD patients in clinical trials.[6] ESS was chosen as the key secondary endpoint as sleep problems are associated with dopamine agonists, are dose-related, and emerge within a short period of time. Impulse control disorders were evaluated, but not selected as the key secondary endpoint as it is less clear that they are dose-related and they typically take months to years to emerge. Long-term studies assessing the effect of P2B001 on impulse control disorders would be of interest, as they cannot be excluded as a side effect of P2B001 based on the present short-term study.[22]

The present study demonstrates that P2B001 provides benefits comparable with commercially used doses of PramiER while minimizing sleep-related and dopaminergic side effects associated with this drug. We did not use a placebo group in the present study as significant benefit of P2B001 compared with placebo has already been demonstrated.[13] The motor benefit observed likely results from the additive effects of the components acting via two different dopaminergic mechanisms (MAO-B inhibition blocks oxidation of dopamine and dopamine agonist act directly on striatal dopamine receptors), whereas the low side effect profile is likely because of the reduced plasma C_{max} and total exposure levels associated with the low doses used. The extended-release formulations of RAS may also have contributed to benefit because of prolonged exposure to rasagiline metabolites, which can potentially provide benefits through non-MAO-B-related mechanisms.[23-25] Indeed, preclinical studies in MPTP mouse model and 6-OHDA rat model demonstrated superior pharmacologic and motor benefits in comparison to the standard formulation of the drugs (data on file at Pharma Two B). The magnitude of benefit compared to placebo in untreated patients with PD previously observed with P2B001 in double-blind trials (~4.7 points)[14] is clinically meaningful,[21,26] and compares favorably with the benefit achieved with dopamine agonists and even the low doses of L-dopa that are typically used in early PD.[3]

We hypothesized that because the drugs act through different mechanisms they might have additive or synergistic anti-parkinsonian benefits, and because they are administered in low doses would have a good safety profile. The data in the present study were generated after publication of the American Academy of Neurology guidelines on initiating treatment in early PD patients,[11] The present evidence supports the consideration of P2B001 as an alternate approach for initiating treatment in early PD, although long-term studies are required. Starting treatment with P2B001 would be expected to provide comparable efficacy to a dopamine agonist, but with reduced sleep-related and dopaminergic side effects and a safety profile like rasagiline, but with superior efficacy. Further, P2B001 requires once-a-day dosing without the need for titration. Additionally, starting treatment with P2B001 delays the introduction of L-dopa, which may have benefits with respect to the risk of developing motor complications,[6,7] although this was not confirmed in the open label pragmatic Parkinson's Disease Medication (PD-MED) study.[27] P2B001, therefore, represents a novel and easy to use therapeutic approach for treating early PD patients that should be appealing to patients, neurologists, and particularly non-specialists who are often the only physicians to treat PD patients.[28]

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Data Availability Statement

Where patient data can be anonymized, Pharma Two B will share the summary tables that underlie the results reported in this article with qualified researchers who provide a valid research question and following a signed data access agreement. Study documents, such as the clinical study report, are not always available.

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Appendix

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

C.W.O., A.M., and K.K. were involved in the study design. R.A.H., D.B., R.D., J.A.d.M., R.A.G., D.L.K., and L.E. were study investigators involved in data collection. C.W.O. wrote the first draft of the article. All authors contributed to the writing and revision of the manuscript and approved the final article for submission. Details of the P2B001 Study Group are provided in the supporting information Supplementary Data S1.

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C.W.O. and K.K. have stock ownership in Clintrex, which was contracted by Pharma Two B to provide services for this study and provides services for multiple other pharmaceutical and biotech companies. C.W.O. has also testified as an expert witness in the paraquat litigation. R.A.H., D.B., R.D., J.A.d.M., R.A.G., D.L.K., and L.E. were investigators in the study and they or their institution received payment from Pharma Two B. R.A.H. is supported in part by a Center of Excellence grant from the National Parkinson Foundation and is employed by the University of South Florida (Florida). He reports receiving personal fees from Acadia Pharmaceuticals, Acorda therapeutics, Adamas Pharmaceuticals, Affiris, AlphaSights, Amneal Pharmaceuticals, ApoPharma, Aptinyx, Aranca, Axovant, Britannia, Cadent, CAVR, Cerevel Therapeutics, ClearView Healthcare Partners, Clinical Score LLC, CNS Ratings LLC, Compass Group, Decision Resource Group (DRG), Dedham Group, Defined Health, Denali, Enterin, Extera Partners, F. Hoffmann-La Roche, First Word, Gerson Lehman Group (GLG), Global Kinetics Consulting (GKC), Global Life Sciences, Guidepoint Global, Huron, Impax Laboratories, Impel Neuropharma, Inhibikase, InSearch Consulting, Insignia Strategies, In-Trace Medical Systems, ISCO, IQVIA, Jazz Pharmaceuticals, Kaiser Permanente, Kashiv Pharma, KeiferRX LLC, KeyQuest, KX Advisors, Kyowa Kirin Pharmaceuticals, L.E.K Consulting, LifeSciences Consultants, Lundbeck A/S, Medscape, MJFF, MPTA, Neuro Challenge Foundation for PD, Neurocrine Biosciences, NeuroDerm, NOVUS, Orion, Parkinson Study Group, Pennside Partners, Perception OpCo, Pharmather, Pharma Two B, PSL Group, Regenera Pharma, Revance Therapeutics, Schlesinger Associates, Scion NeuroStim LLC, Seelos Therapeutics, Slingshot Insights, Sunovion Pharmaceuticals, Supernus Pharma, Teva Pharmaceuticals, Tolmar, and US World Meds. R.A.H. reports research support from AbbVie, Axovant Sciences, Biogen, Biotie Therapies, Cavion, Centogene, Cerevance, Cerevel Therapeutics, Cynapsus Therapeutics, Enterin, F. Hoffman-La Roche, Global Kinetics Corporation (GKC), Impax Laboratories, Intec Pharma, Jazz Pharmaceuticals, The Michael J. Fox Foundation, Neuraly, NeuroDerm, Northwestern University, Pfitzer, Pharma Two B, Revance Therapeutics, Sanofi US Services, Sun Pharma Advanced Research Company, Sunovion Pharmaceuticals, and holds stock in Inhibkase and Axial Therapeutics. The institution of D.B. has received funding in support of clinical trials from Merck, Praxis Precision Medicines, Jazz Pharmaceuticals, Cerevel Therapeutics, Athira Pharma, Neuraly, AbbVie, Enterin, Amneal, Acorda Therapeutics, and Intec Pharma. R.D. has received consulting fees from CalaHealth, Best Doctors, MD Edge, Acorda Therapeutics, and Pharma Two B. The institution of R.D. has received funding in support of clinical trials from Praxis Precision Medicines, Cerevel Therapeutics, Neuraly, AbbVie, Parkinson Study group, NeuroDerm, Global Kinetics Corp, CalaHealth, and Amneal. D.L.K has been an investigator in clinical trials sponsored by Amneal, Acadia, Pharma2b, UCB, Biotie, Lundbeck, Pfizer, Addex, and Neurocrine. D.L.K. served on an advisory boards sponsored by Amneal, Acorda, Cerevel, Acadia, US WorldMeds, and Neurocrine, and is on the following Speakers' Bureau; Acadia, Amneal, Acorda, Adamas, Kyowa Kirin, Neurocrine. L.M.E. has received clinical trial grant support, serves as a scientific manuscript author, and/or speaker's board member for the following pharmaceutical companies; Vaccinex (Huntington Study Group), Cynapsus Therapeutics, Lundbeck Pharmaceuticals, Pharma Two B, Impax Laboratories, Prilenia Therapeutics, Enterin, Acadia Pharmaceuticals, Neuraly, NeuroDerm, Cerevel Therapeutics, Neurocrine Biosciences, Addex Pharmaceuticals, and Teva Pharmaceuticals.