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COMMENTARY

P2B001 (Extended Release Pramipexole and Rasagiline): A New Treatment Option in Development for Parkinson's Disease

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ABSTRACT

Despite levodopa's superior efficacy in reducing the motor symptoms of Parkinson's disease (PD), its risk to induce motor complications requires consideration of the pros and cons of initiating treatment with levodopa-sparing strategies. The current drive toward early levodopa monotherapy is primarily driven by safety and tolerability concerns with dopamine agonists and only mild efficacy of other available approaches. Recently, P2B001, a novel once-daily combination of low-dose, extended-release formulations of pramipexole and rasagiline (0.6 mg and 0.75 mg respectively), has entered clinical development. In this drug evaluation, we review the preclinical and current clinical data for P2B001 and its components. The P2B001 combination has the potential to provide greater efficacy than either pramipexole or rasagiline alone and a better tolerability profile compared to higher dosage dopamine agonist monotherapy, while maintaining the advantage of lower motor complication risk than levodopa.

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PLAIN LANGUAGE SUMMARY

Parkinson's disease is the fastest growing neurologic disorder across the globe. Once diagnosed, it is now generally agreed that there is no clinical rationale to postpone symptomatic treatment in people who develop Parkinson's-related disability. There are three main treatment options available for use in early Parkinson's disease: levodopa, dopamine agonists and monoamine oxidase type B (MAO-B) inhibitors. Of these, there is a current push toward using levodopa as the main first-line therapy. This is primarily because of the significant safety and tolerability concerns with dopamine agonists and only mild efficacy of MAO-B inhibitors.

Recently, P2B001, a novel drug formulation combining once-daily, extended-release, low dosages of the dopamine agonist pramipexole and the MAO-B inhibitor rasagiline (0.6 mg and 0.75 mg respectively), has entered clinical development. In this article, the authors review the preclinical and current clinical data on P2B001 and its components. The P2B001 combination has the potential to provide greater efficacy than either pramipexole or rasagiline alone and a better tolerability profile compared to higher dosage dopamine agonist monotherapy, while maintaining the advantage of lower motor complication risk than levodopa.

Keywords: Combination therapy; P2B001; Parkinson's disease; Pramipexole; Rasagiline; Treatment

Key Summary Points

P2B001 is in development as once-daily monotherapy for the treatment of the signs and symptoms early Parkinson's disease.

P2B001 is a novel, fixed-dose, once-daily combination of extended-release formulations of pramipexole and rasagiline (0.6/0.75 mg), both components at low doses that are not individually available on the market.

The combination of pramipexole and rasagiline aims to improve striatal dopaminergic transmission via distinct and potentially synergistic mechanisms.

Phase 2 data demonstrated significant symptomatic efficacy of P2B001 versus placebo, with a benign safety profile that was similar to placebo.

INTRODUCTION

Parkinson's disease (PD) is the fastest growing neurologic disorder across the globe [1]. It has been estimated that in 2016 there were approximately 6.1 million people living with the disease [2], with a life-time risk of PD as high as 1 in 15 [3]. A rapid increase in prevalence is not solely due to an aging population, but also due to increasing life expectancy [2, 3] and thus longer disease durations than in previous years. One French study estimated that by 2030 PD patients aged 65 will live an extra 3 years compared to patients in 2010 [4]. While the prevalence of PD increases steadily with age, almost a quarter of those affected had onset before the age of 65 years old [5, 6], with the implication that these patients can be expected to live for many years with the disease.

Once diagnosed, it is now generally agreed that there is no clinical rationale to postpone symptomatic treatment in people who develop PD-related disability [6]. Conventional pharmacotherapy for motor symptom control is primarily based on dopaminergic replacement strategies [6, 7]. Current European guidelines recommend levodopa, dopamine agonists and monoamine oxidase type B (MAO-B) inhibitors as having Level A evidence for the treatment of early untreated PD [8, 9]. The choice of first drug is left to clinical judgment depending on the need for symptomatic efficacy in improving motor disability (lowest with MAO-B inhibitors and highest with levodopa) compared with the risks of developing motor-complications (highest for levodopa) or risks for daytime somnolence, hallucinosis and problems with impulse control (lowest for MAO-B inhibitors and highest for dopamine agonists) [8, 9]. By contrast, the recent American Academy of Neurology (AAN) guidelines [10] recommend levodopa as the initial therapy for most patients with early PD seeking treatment for motor symptoms. While dopamine agonists should be avoided in subjects at high risk for dopaminergic adverse events (AEs), including patients aged > 70 years, those with a history of impulse control disorders (ICDs) or pre-existing excessive daytime sleepiness, cognitive impairment

and hallucinosis, they may still be used in select patients aged $\leq$ 60 years who are at higher risk for the development of dyskinesia [10].

Despite levodopa's superior efficacy in reducing the motor symptoms of PD [11, 12], its risk to induce motor complications requires consideration of the pros and cons of initiating treatment with levodopa-sparing strategies. Although their effect size in reducing motor symptoms is inferior to levodopa overall, dopamine agonists may provide satisfactory symptom control in early disease for several years and dopamine agonist monotherapy has a very low risk to induce motor complications [11, 12]. Likewise, in the early disease stages, when patients present with mild motor symptoms, MAO-B inhibitors may also provide sufficient benefit with low risk for adverse events [13]. Both of these levodopa-sparing approaches offer opportunity for once-daily drug regimens, which are more convenient for patients and have been shown to enhance adherence [14].

While early combination therapy approaches were initially explored for levodopa and dopamine agonists (with and without MAO-B inhibition) in the 1980s [15–17], the use of initiating treatment with drug combinations has since been neglected in clinical research and the potential benefits of combining drugs with different mechanisms of action have remained largely unexplored. Recently, a novel drug formulation combining an MAO-B inhibitor with a low-dose dopamine agonist has entered clinical development [18]. This combination has the potential to provide greater efficacy than either agent alone and a better tolerability profile compared to higher dosage dopamine agonist monotherapy, while maintaining the advantage of lower motor complication risk than levodopa. In this drug evaluation, we review the data for P2B001, which combines lower than currently used doses of extended release (ER)-pramipexole and ER-rasagiline (0.6 mg and 0.75 mg, respectively) and is under development for patients with early PD.

INTRODUCTION TO P2B001 AND ITS COMPONENTS

P2B001 is a combination capsule developed to slowly release ER-pramipexole and ER-rasagiline simultaneously throughout the day. As will be discussed below, both components have a large evidence base supporting their efficacy. Whereas pramipexole provides the stronger symptomatic effect of the two, its use is limited by the development of dose-related adverse events [19]. Therefore, the P2B001 ER-pramipexole component dose is limited to 0.6 mg/day. Whereas rasagiline has a safety profile similar to placebo, its use as monotherapy is often short-lived because of mild efficacy in the face of a progressive disease. The combination of pramipexole and rasagiline was chosen for clinical development because they are thought to act in potentially complementary mechanisms [20, 21].

CHEMISTRY AND PHARMACODYNAMICS OF P2B001 COMPONENTS

Pramipexole

Pramipexole is a full, nonergot dopamine agonist with high relative in vitro specificity and full intrinsic activity at the dopamine $D_{2\text{-like}}$ subfamily of dopamine receptors, binding with higher affinity for D_3 than to D_2 or D_4 receptor subtypes (Ki's of 0.5 nM vs. 3.3–3.9 nM, respectively) [22–24]. The ratio of selectivity for binding to D_3 over D_2 is about 6.5–8, with some evidence of selectivity in functional assays [24]. Affinity for D_1 receptors is insignificant, being around 200,000 times lower than that to D_3 receptors [23]. Pramipexole may have multiple mechanisms of action that are not fully elucidated. However, it is known that pramipexole acts on presynaptic as well as postsynaptic dopamine receptors [23]. Whereas in the intact striatum stimulation of presynaptic autoreceptors of the D_3 and D_2 type is thought to reduce the synthesis and synaptic release of dopamine [25], in the parkinsonian state, the postsynaptic

D_3 and D_2 receptors on the striatofugal neurons of the direct and indirect pathways are additionally stimulated. It is hypothesized that, in the parkinsonian state, pramipexole corrects the increased inhibitory impact of the direct pathway on motor activity by enhancing the direct transmission (through D_3 receptors) and reducing the indirect transmission (through D_2 receptors), thereby mimicking dopamine's effects in the striatum [26]. Several potential mechanisms for neuroprotection have also been proposed [27–29]; however, the PRIDE delayed-start study did not find evidence of a disease-modifying effect for pramipexole monotherapy [30].

The symptomatic efficacy of pramipexole in early PD is well established [11, 31, 32]. While its effect size is inferior to that of levodopa, pramipexole has a reduced propensity to cause motor complications [11]. This has led to its use as an option for initial monotherapy, especially in younger patients who have greater risk to develop dyskinesias in response to levodopa. However, there are safety concerns, including the induction of daytime sleepiness and sudden-onset sleep as well as ICDs. These side effects are often dose-related, with higher doses resulting in a higher risk compared with small to medium doses [33–36].

Rasagiline

Rasagiline (N-propargyl-1-(R)-aminoindan) is a potent and irreversible inhibitor of MAO-B, which is attributed to irreversible covalent binding of its propargyl moiety to the flavin adenine dinucleotide (FAD) moiety of the enzyme. By binding to the FAD moiety, rasagiline prevents the access of dopamine to MAO-B, thereby inhibiting oxidative deamination to 3,4-dihydroxphenlyacetic acid (DOPAC) and raising the levels of dopamine [37]. MAO-B inhibition with rasagiline also increases the availability of phenylethylamine, which can enhance striatal dopamine release [38]. Striatal dopamine release may also be enhanced by the rasagiline active metabolite, 1-aminoindan, an effect which is thought to be separate from MAO-B inhibition (although 1-aminoindan is also a weak MAO-B inhibitor) [39, 40]. Both rasagiline and 1-aminoindan contain a propargylamine moiety which have been shown to inhibit apoptosis in both in vitro and in vivo models of PD [41]. Such effects are thought to be driven at the mitochondrial level where propargylamine inhibits apoptotic pathways, induces glial cell-derived neurotrophic factor (GDNF) and brain cell-derived neurotrophic factor (BDNF), and stimulates protein kinase C phosphorylation [42].

The symptomatic efficacy and safety of rasagiline monotherapy in early disease has also been firmly established by randomized controlled trials (RCTs) [13, 43]. The effect size is mild, but in early disease, rasagiline monotherapy has been sustained for years without the need for adjunct medications in a sizable proportion of subjects [44]. Rasagiline monotherapy is generally very well tolerated with little difference in the rate of adverse events between rasagiline and placebo [13, 43]. In addition, the neuroprotective properties of rasagiline seen in preclinical studies [42] did not readily translate to the clinic where one large randomized, delayed-start design trial of rasagiline monotherapy found that rasagiline 1.0 mg, but not 2.0 mg, had statistically significant effects on clinical progression [13].

PHARMACOKINETICS AND METABOLISM OF P2B001

P2B001 contains both pramipexole and rasagiline formulated using a proprietary ER coating system. While ER pramipexole formulations have been available for over a decade, P2B001 contains the first ER formulation of rasagiline and is, additionally, the first combination of both.

Pramipexole has an absolute oral bioavailability > 90%, with steady absorption across the intestine and little first pass metabolism [26]. It exhibits linear pharmacokinetics, and < 20% is protein bound; > 90% of the absorbed dose is eliminated unchanged and almost exclusively by the kidneys. Rasagiline is rapidly absorbed, reaching peak plasma concentration (C_{max}) in approximately 1 hour. The absolute

bioavailability of rasagiline is about 36%, and plasma protein binding ranges from 88 to 94% with mean extent of binding of 61–63% to human albumin over the concentration range of 1–100 ng/ml [45]. At steady state, the mean AUC and C_{max} for rasagiline and 1-aminoindan are linearly proportional to the rasagiline dose [46]. Rasagiline undergoes almost complete biotransformation in the liver prior to excretion. The metabolism of rasagiline proceeds through two main CYP-450-dependent pathways: *N*-dealkylation and/or hydroxylation to yield 1-aminoindan (major active metabolite), 3-hydroxy-*N*-propargyl-1-aminoindan and 3-hydroxy-1-aminoindan. Glucuronide conjugation of rasagiline and its metabolites, with subsequent urinary excretion, is the major elimination pathway. There is no correlation of pharmacokinetics with the MAO-B inhibition of rasagiline because of its irreversible inhibition of MAO-B. However, it is hypothesized that other mechanisms of efficacy (e.g., via 1-aminoindan [47, 48]) may be in effect, which may be better leveraged by using an extended-release formulation.

A comparative bioavailability study was performed in 22 healthy volunteers (aged 18–-55 years) to assess the relative rasagiline and pramipexole systemic exposure of P2B001 under fasting conditions. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines, and all participants provided written informed consent. The randomized, single-dose, crossover study compared a single dose of P2B001 (0.6 mg ER-pramipexole/0.75 mg ER-rasagiline) with the combination of branded pramipexole-ER (Mirapex ER®, Boehringer Ingelheim, Germany) plus branded rasagiline (Azilect®, Teva Pharmaceuticals, Israel) at currently used doses (0.75 mg and 1 mg, respectively). The overall pharmacokinetic profile of the P2B001 pramipexole component was similar to that seen with the branded pramipexole-ER plus rasagiline combination (albeit with lower C_{max} and AUC due to lower dosing), while the C_{max} of the P2B001 rasagiline component was significantly lower (from 5774 to 537 pg/ml) and the $t_{1/2}$ significantly longer (from 3.9 to 12.5 h) than that obtained with the branded rasagiline due to the extended-release formulation (Fig. 1A, Table 1).

Thus, both drug components in P2B001 are slowly released simultaneously throughout the day. This profile reflects the desired change to an ER rasagiline formulation in which C_{max} is significantly lower (important for safety), a sharp peak is avoided, and the half-life is extended while maintaining a comparable AUC. Moreover, the findings support the safety profile of P2B001 as the overall exposure is lower than the component products with established safety profiles. At steady state, the C_{max} and AUC of both rasagiline and pramipexole are approximately twofold higher than after the first dose of P2B001. In a 7-day multidose study also conducted in healthy volunteers (n = 20), both the pramipexole and rasagiline components of P2B001 reached steady state after 5 days of administration (Fig. 1B).

P2B001 CLINICAL EFFICACY

Phase II Clinical Study of Two Doses of P2B001 Versus Placebo

The efficacy and safety of the current P2B001 formulation (0.6 mg pramipexole-ER/0.75 mg rasagiline) and a lower pramipexole dose formulation (0.3 mg ER-pramipexole/0.75 mg ER-rasagiline) were tested in a Phase II 12-week multicenter double-blind, placebo-controlled clinical trial [18]. In this study, untreated patients with early PD were randomized to once-daily treatment with P2B001 (0.3 mg ER-pramipexole/0.75 mg ER-rasagiline), P2B001 (0.6 mg ER-pramipexole/0.75 mg ER-rasagiline) or placebo [18].

The placebo-adjusted mean change from baseline to Week 12 in Total Unified Parkinson's Disease Rating Scale (UPDRS) score (parts I + II + III, primary end point) was − 4.7 points for the P2B001 0.6/0.75 mg group (P = 0.0004) and − 3.8 points for the P2B001 0.3/0.75 mg group (P = 0.003). Differences versus placebo were seen as early as Week 4 for both dosages of P2B001 (Fig. 2). The placebo-adjusted magnitude of change for the 0.6/0.75 mg dose group is

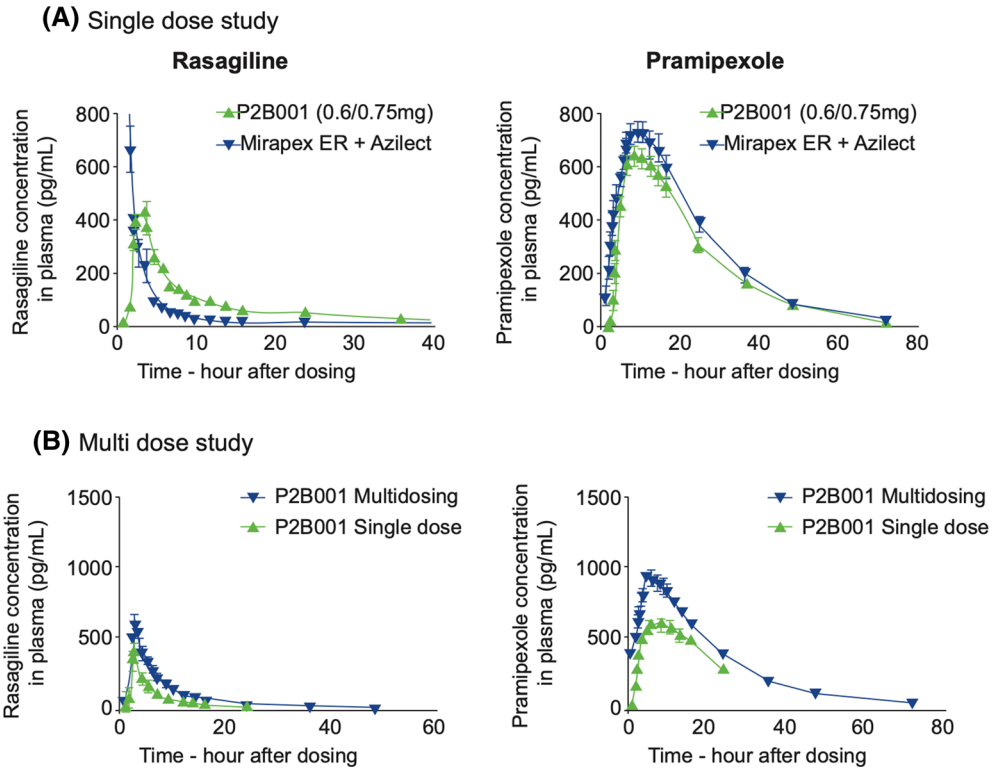

Fig. 1 Plasma concentrations of rasagiline and pramipexole during **A** the 72-h following single-dose administration of P2B001 (0.6/0.75 mg) or Mirapex ER + Azilect (0.75/1.0 mg); **B** during the 24 h following single-dose administration of P2B001 on day 1 and during the 72-h following the final dose on day 7 for multiple-dose administration of P2B001

Table 1 Comparative pharmacokinetics of P2B001 components versus branded products

	C_{max} (pg/ml)	T_{max} (h)	AUC_{0-inf} (h*pg/ml)	$t_{½}$ (h)
Pramipexole-ER (0.75 mg) + Rasagiline (1 mg) (N = 19)	PPX: 804 ± 222	PPX: 9.1 ± 3.4	PPX: 21,451 ± 5388	PPX: 12.2 ± 2.5
	RAS: 5774 ± 2447	RAS: 0.6 ± 0.3	RAS: 4680 ± 1573	RAS: 3.9 ± 1.6
P2B001 (0.6/0.75 mg) (N = 19)	PPX: 765 ± 227	PPX: 7.7 ± 2.9	PPX: 18,480 ± 5182	PPX: 14.6 ± 3.9
	RAS: 537 ± 256	RAS: 2.5 ± 0.5	RAS: 3000 ± 715	RAS: 12.5 ± 7.3

All data are mean ± SD

considered clinically relevant [49] and was higher (5.7 points in the P2B001 0.6/0.75 mg group and 4.6 points in the P2B001 0.3/0.75 mg group) when an outlier site that recorded marked placebo effects was excluded in post hoc analysis [18]. Moreover, the symptomatic benefits observed with P2B001 compare well with the efficacy reported in randomized, placebo-

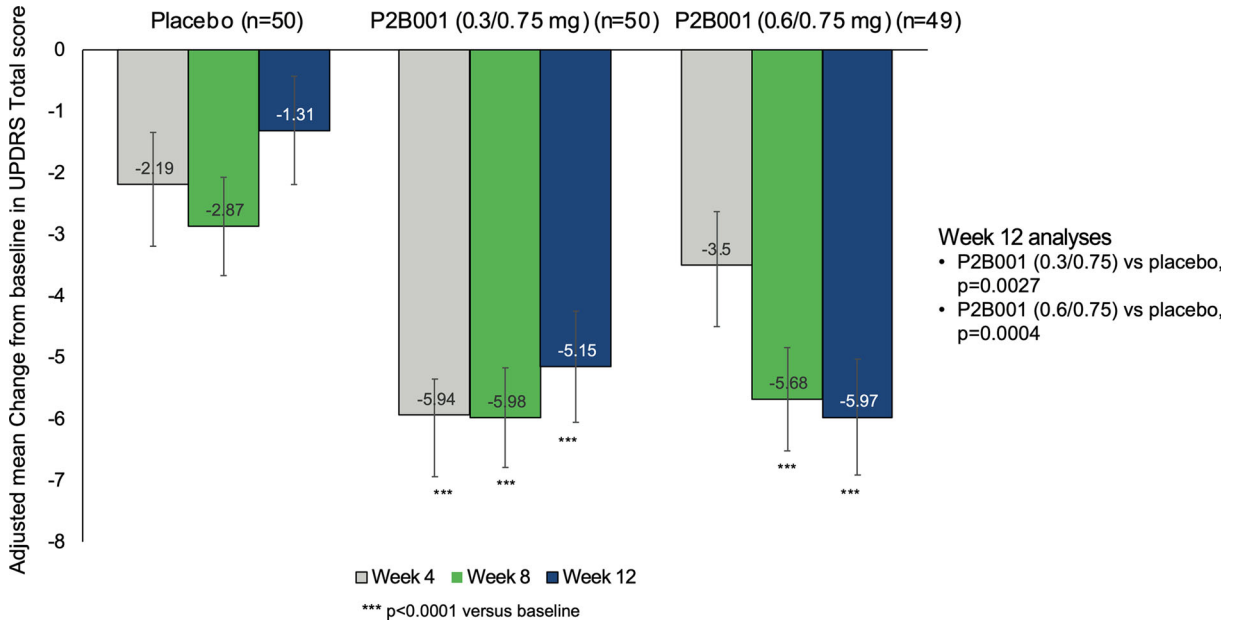

Fig. 2 Adjusted mean change from baseline in Total UPDRS (Parts I + II + III) scores in the phase 2 clinical trial. *UPDRS, Unified Parkinson's Disease Rating Scale*

controlled trials of the marketed higher dose of the separate components. For example, treatment with pramipexole (1.5 mg/day) improved Total UPDRS scores by 5.2 points versus placebo at Week 10 in the STEP-UP clinical trial [50] and by 4.8 points at 9 months in the PROUD study [51]. Similarly, in the pramipexole PRAMI-BID study, patients treated with pramipexole (1–-1.5 mg/day) showed placebo-adjusted improvements of 4.4–4.7 Total UPDRS points at Week 12 [52]. Treatment with rasagiline (1 mg/day) improved Total UPDRS scores by 4.2 points versus the placebo group (which showed significant worsening over time) at Week 26 of the TEMPO study [53] and by 3.0 points at ~ Week 36 in the ADAGIO study [13].

The significant effects of the 0.6/0.75 mg dose of P2B001 on quality of life also compares favorably with the results seen with pramipexole monotherapy in the PRAMI-BID study [52]. Whereas treatment with P2B001 (0.6/0.75 mg) significantly improved PDQ-39 Total (treatment effect of -3.3 ± 1.2 points vs. placebo; $P = 0.01$), ADL (-7.2 ± 2.0 points vs. placebo, $P = 0.0005$) and Mobility (-4.7 ± 1.8 points vs. placebo $P = 0.01$) scores [18], these benefits were only achieved in the PRAMI-BID study when pramipexole was given at the higher daily dose of 1.5 mg/day (treatment effect of 2.1 points on PDQ-39 Total scores vs. placebo when given 0.75 mg BID or 0.5 mg TID, $P \leq 0.05$). Effects on PDQ-39 Total scores were not significantly different from placebo for the pramipexole 1.0 mg/day (0.5 mg BID) dose group ($P = 0.32$) [52].

Phase III Clinical Study Comparing P2B001 with its Individual Components

The efficacy and safety of the 0.6/0.75 mg dose have recently undergone further evaluation in a Phase III randomized, pivotal study (NCT03329508). To answer the question of how P2B001 compares to its individual ER components, 544 eligible subjects with early untreated PD were randomized (2:2:2:1) to 12-week double-blind treatment with once-daily P2B001, pramipexole-ER (0.6 mg once daily) alone, rasagiline-ER (0.75 mg once daily) alone or currently marketed pramipexole-ER titrated to optimal dose (active calibration arm; 1.5, 3.0 or

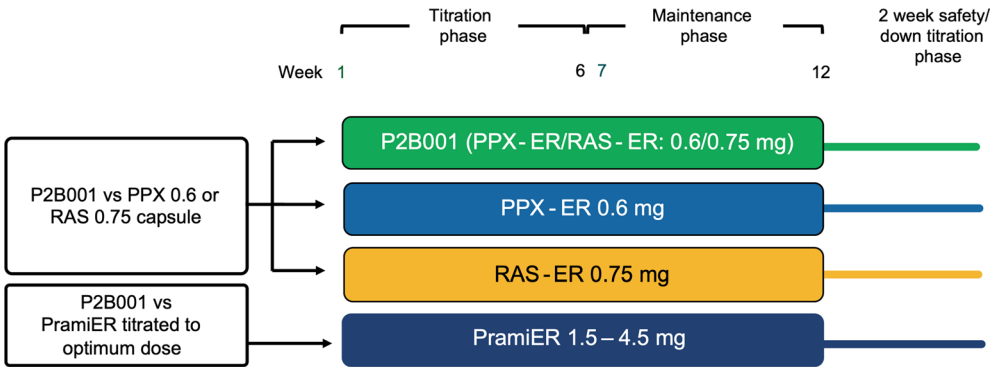

Fig. 3 Phase III, double-blind, double-dummy, parallel group study design. *PPX, pramipexole; PramiER, branded pramipexole extended release; RAS, rasagiline*

4.5 mg) (Fig. 3). The primary efficacy endpoint compares the change from baseline to Week 12 in UPDRS-Total score (Parts II + III) for P2B001 with its individual components. The first secondary endpoint compares the change from baseline in Epworth Sleepiness Scale (ESS) for P2B001 versus titrated pramipexole-ER. Sample sizes were estimated separately for the primary and secondary endpoints, with a smaller sample required for the secondary endpoint.

At the time of this manuscript's submission, the sponsors had just announced that the study met its primary objective showing superiority of P2B001 0.6/0.75 mg compared to its individual components in the change of Total UPDRS (parts II + III) score. Secondary objectives were also met, including significantly less daytime sleepiness (somnolence) compared to a currently marketed pramipexole-ER [54]. Full peer-reviewed details of this study have not yet been published.

Safety and Tolerability of P2B001

In terms of safety and tolerability, as reported in the Phase II study, P2B001 was well tolerated with an adverse event profile similar to placebo, with the exception of mild and transient nausea and somnolence, known adverse events of pramipexole [18], although somnolence was not significantly different than for placebo when evaluated using the ESS.

Somnolence, which can lead to falls, injury and difficulties driving [33], is a common occurrence in patients receiving pramipexole at doses > 1.5 mg/day (0.5 mg TID) for PD [55]. While somnolence was experienced more frequently with P2B001 than placebo in the Phase II study [18], its incidence was lower than experienced across the pramipexole pivotal studies in early PD (16% with P2B001 [18] and 22% with pramipexole [55]). Indeed, placebo-adjusted changes from baseline in ESS score with P2B001 were comparable to placebo and less than has been reported with higher doses of pramipexole in early PD (0.5 vs. 1.0–2.1) in early PD [52, 56, 57]. While the proportion of patients who shifted to having an ESS score > 10 was similar for P2B001 (0.6/0.75 mg) to placebo (both 6%), it was less than the 16% reported with pramipexole-IR and 21% with pramipexole-ER (versus 8% with placebo) across earlier studies with pramipexole [58].

Table 2 compares the safety and tolerability of P2B001 (0.6/0.75 mg) in the phase II trial [18] with the safety of pramipexole in previous placebo-controlled studies of similar duration [50, 52]. There were no reports of ICDs, hallucinations or psychosis with P2B001 in the 12-week Phase II study [18]. While hallucinations were already seen in > 5% of patients treated with pramipexole 1.5 mg within 10 weeks of the STEP-UP study [50] and in 16.5% of patients receiving pramipexole (up to 4.5 mg/day) across the early PD pivotal trials [55], these psychiatric adverse events often

Table 2 Adverse events reported with P2B001 in the Phase II study compared with data from previous randomized, placebo-controlled trials of pramipexole

Adverse event	P2B001 Phase II Study [18]		STEP-UP Pramipexole Study [50]			Pramipexole PRAMI-BID Study [52]			
	Placebo	P2B001 (0.6/ 0.75 mg)	Placebo *n* = 51	Pramipexole (1.5 mg) *n* = 54	Pramipexole groups combined (1.5–6 mg) *N* = 213	Placebo *N* = 77	Pramipexole (0.5 mg BID) *n* = 81	Pramipexole (0.75 mg BID) *n* = 73	Pramipexole (0.5 mg TID) *n* = 80
Nausea	1 (2.0)	10 (20.4)	5 (9.8)	9 (16.7)	42 (19.7)	8 (10.4)	18 (22.2)	11 (15.1)	15 (18.8)
Somnolence	0	8 (16.3)	7 (13.7)	9 (16.7)	58 (27.2)	5 (6.5)	14 (17.3)	16 (21.9)	20 (25.0)
Dizziness	4 (8.0)	5 (10.2)	10 (19.6)	10 (18.5)	39 (18.3)	7 (9.1)	9 (11.1)	5 (6.8)	9 (11.3)
Fatigue	1 (2.0)	4 (8.2)	5 (9.8)	4 (7.4)	14 (6.8)	3 (3.9)	6 (7.4)	7 (9.6)	4 (5.0)
Insomnia	2 (4.0)	3 (6.1)	4 (7.8)	2 (3.7)	16 (7.5)	4 (5.2)	3 (3.7)	11 (15.1)	6 (7.5)
Orthostatic hypotension	4 (8.0)	2 (4.1)	NR	NR	NR	NR	NR	NR	NR
Headache	4 (8.0)	1 (2.0)	5 (9.8)	5 (9.2)	24 (11.3)	8 (10.4)	7 (8.6)	6 (8.2)	4 (5.0)
Hallucination	0	0	0	4 (7.4)	14 (6.6)	NR	NR	NR	NR
Constipation	1 (2.0)	1 (2.0)	3 (5.9)	4 (7.4)	23 (10.8)	2 (3.9)	8 (9.9)	7 (9.6)	5 (6.3)
Confusion	0	0	0	3 (5.6)	9 (4.2)	NR	NR	NR	NR
Abnormal dreams	0	0	NR	NR	NR	3 (3.9)	3 (3.7)	2 (2.7)	5 (6.3)
Peripheral edema	0	0	NR	NR	NR	0	2 (2.5)	4 (5.5)	3 (3.8)

NR, not reported

develop over a longer time frame with higher doses of pramipexole, and a longer duration of observation is required before drawing firm conclusions. Headache was one of the most common adverse events leading to study discontinuation in the pramipexole trials [55], but was only experienced by one patient receiving P2B001 (0.6/0.75 mg) in the Phase II study [18].

These data suggest that a low-dose, extended-release combination of pramipexole and rasagiline may be a safe and effective way to initiate therapy for patients with early PD. Patients who do not yet require levodopa therapy may prefer to take a once daily medication that offers good symptom control with an adverse event profile similar to placebo.

Regulatory Affairs

Following the positive findings of the Phase III study [54], a new drug application for P2B001 as a treatment for patients with early PD (newly diagnosed and early-stage disease) will be submitted to the US Food and Drug Administration (FDA) in 2022. Marketing approval will then be sought in Europe and the rest of the world.

POTENTIAL ROLE FOR P2B001 IN EARLY PARKINSON'S DISEASE

The therapeutic potential of polytherapy using fixed combinations of agents with established symptomatic efficacy has remained virtually unexplored in the field of PD. In principle, combination therapies offer the potential of mechanistic synergy with efficacy going beyond that provided by individual components. As seen in other fields of medicine [59, 60], combining mechanisms of action offers the opportunity for dose saving, which in itself can improve safety and tolerability. In the case of P2B001, the aim is to leverage the complementary mechanisms of rasagiline and pramipexole in early PD, where the patient's remaining central dopamine reserves are enhanced by MAO-B inhibition with rasagiline while pramipexole provides prolonged dopamine receptor stimulation. When given at doses that would be considered 'submaximal' as separate agents, together they have been shown to provide clinically relevant efficacy with a low propensity for adverse events [18].

The major concern that has limited the use of dopamine agonists in recent years relates to their potential to induce ICDs, which may affect 10–40% of patients depending on patient characteristics, dose and concomitant medications [36]. Since ICDs are particularly common with high-dose agonist therapy [35, 36], the dose savings afforded by a combination with a second dopaminergic drug can be expected to significantly lower the ICD and somnolence risks of pramipexole, and this likely applies to hallucinosis as well. Safety data from the ongoing P2B001 studies have been favorable in this regard, but long-term data will be important for a full risk–benefit assessment.

An important advantage to any approach to initiate therapy in PD is the possibility of a once-daily mode of administration—from both the perspective of convenience and adherence. Given its once-daily formulation, lack of titration and favorable side effect profile, P2B001 may be an attractive option for newly diagnosed patients, who often resist the idea of having to take their medication at least three times a day. In the longer term, initial therapy is expected to require levodopa supplementation to maintain sufficient motor symptom control, although a longer follow-up (than in the current studies) will be needed to understand the amount of time P2B001 can be used as a monotherapy. This will likely require lower doses compared to initial levodopa monotherapy and thus be associated with a lower risk of or longer delay to development of motor complications. Beyond its use as initial therapy in early PD, P2B001 seems worth investigating as an adjunct to levodopa in patients experiencing motor fluctuations. Both components have been shown to reduce motor fluctuations as adjunct therapies at higher doses, and their combined use at low dose might offer similar benefits with improved safety in this indication as well.

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Data Availability. Data for the pharmacokinetic study are available from the corresponding author on reasonable request. Full protocol details for the phase III study are available at clinical trials.gov: https://clinicaltrials.gov/ct2/show/NCT03329508.

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