P2B001 significantly reduced risk of daytime sleepiness: results from a randomized controlled phase 3 trial with active pramipexole arm in early Parkinson's disease (PD)

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Introduction and objectives

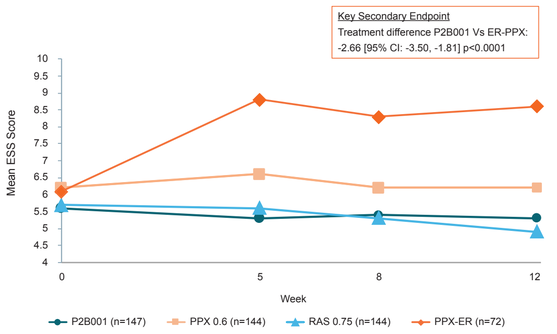
- The choice of initial therapy for Parkinson's disease (PD) depends on the need for symptomatic efficacy, compared with the risks of developing motor-complications or risks for common dopaminergic side effects.
- While recognizing the clear limitations of levodopa, current AAN guidelines[1] have recently moved away from recommending dopamine agonist monotherapy, primarily due to the risks of dose-related side effects such as daytime sleepiness, impulse control disorders, cognitive impairment and hallucinosis.
- P2B001 is an investigational, fixed-dose, once-daily combination of extended release (ER) formulations of pramipexole and rasagiline (0.6mg/0.75mg), in development as once-daily treatment for the signs and symptoms of PD. The combination of pramipexole and rasagiline aims to improve striatal dopaminergic transmission via distinct and potentially synergistic mechanisms, while the lower doses allow for a favorable safety profile.[2]
- Primary efficacy analyses from this Phase 3 study showed that once-daily, fixed dose P2B001 showed superior efficacy to each of its individual components on change from baseline in UPDRS Total (Parts II+III) scores, and provided comparable efficacy (~8 point reduction) with marketed ER pramipexole (ER-PPX) individually titrated to optimal effect.[3]
- Safety analyses showed that fewer dopaminergic adverse events were reported with P2B001 vs ER-PPX. Here we compare excessive daytime sleepiness (EDS) profiles of P2B001 and Extended-Release pramipexole (ER-PPX) in untreated PD.[3]

Methods

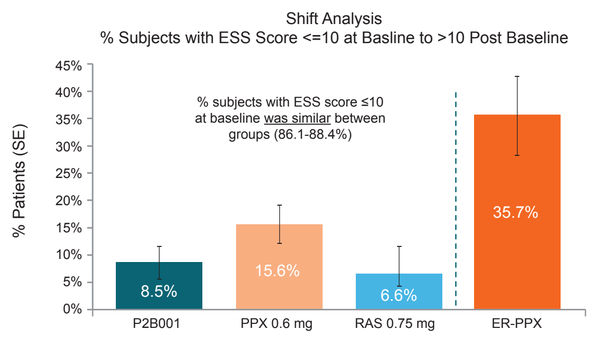
- Untreated patients (time from diagnosis<3 years, Hoehn & Yahr <3) were randomized (2:2:2:1) to 12-weeks double-blind treatment with P2B001, its individual components, or marketed ER-PPX (6-week individual optimal titration).[2,3]
- EDS was assessed by Epworth Sleepiness Scale (ESS; key secondary endpoint) and treatment-emergent adverse event (TEAE) reporting.
- Rates of new-onset clinically-relevant EDS were assessed using shift analysis (from ESS ≤10 at baseline to >10 at Week 12).[4]

Results

Significantly less daytime sleepiness (Epworth Sleepiness Scale [ESS])

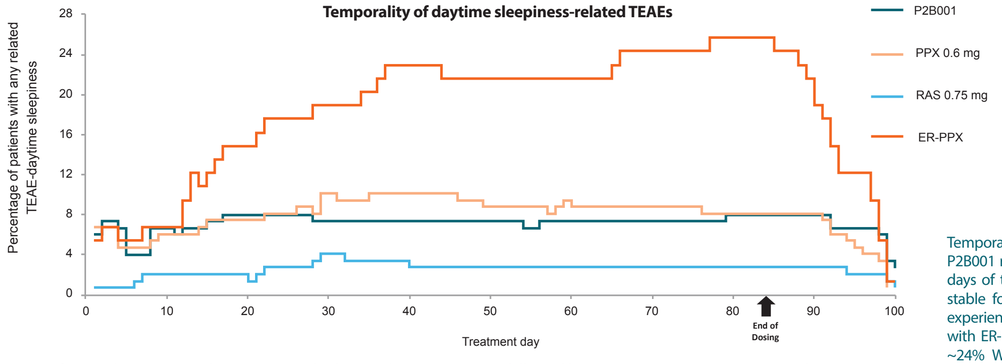


P2B001 showed significantly less subjects shifted to extensive daytime sleepiness compared to ER-PPX



Adjusted odds ratios at Week 12 (P2B0001 vs ER-PPX): 0.166 [0.078, 0.355] (p<0.0001)

Temporality of daytime sleepiness-related TEAEs



Rates of somnolence reported as TEAEs were highest with ER-PPX (31.1%) followed by PPX (18.2%), P2B001 (14.7%) and RAS (4.8%)

Temporally, 6-7% of patients treated with ER-PPX, PPX and P2B001 reported sleepiness-related TEAEs within the first days of treatment. While these rates remained relatively stable for PPX and P2B001, the proportion of patients experiencing daytime sleepiness events steadily increased with ER-PPX titration and maintenance therapy (plateau ~24% Week 6). Daytime Sleepiness Related AEs were predefined as somnolence and sudden onset of sleep.

Conclusions

- The development of dose-related excessive daytime sleepiness is considered a key limiting factor to the utility of pramipexole in early PD.[1]
- The present study demonstrates that P2B001 provides benefits comparable to marketed doses of ER-PPX titrated to individual optimal doses (mean dose 3.2mg/day) while minimizing important daytime sleepiness-related side effects associated with this drug.
- The findings support the potential of P2B001 as a first-line, once-daily treatment for people with PD that may offer effective symptomatic control with a favorable safety profile and no need for titration.

References

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