Improvement of Predominant Negative Symptoms in Patients With Schizophrenia on Paliperidone Palmitate 6-month Long-Acting Injectable: Post-Hoc Analysis Over 3 Years

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Background

- Schizophrenia is a debilitating disorder characterized by persistent negative symptoms, cognitive impairments, and functional deficits that drive long term disability[1, 2]
- Negative symptoms often persist over time, and their remission is critical for meaningful functional recovery[1,3]
- Paliperidone palmitate 6-month long acting injectable (PP6M) has demonstrated noninferior efficacy in preventing relapse compared to paliperidone palmitate 3-month long acting injectable (PP3M) in a pivotal double-blind (DB) study[4], with sustained effect in a 2-year open-label extension (OLE) study[5] in patients with schizophrenia

Objective

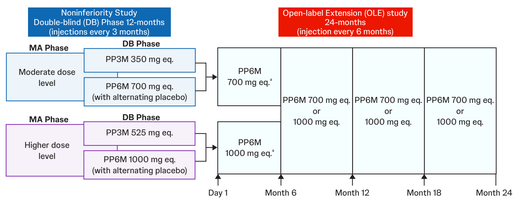
To evaluate the long-term Impact of PP6M on negative symptoms and functional outcomes over 1-3 years in patients with schizophrenia in predominant negative symptom (PNS) population

Methods

Study design

- Adults (aged 18–70 years) with a confirmed diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria and total PANSS <70 at screening maintained through to DB randomization, previously stabilized on PP1M or PP3M in a 12 month phase 3 noninferiority DB study (NCT03345342), who completed the DB phase without relapse, and continued on PP6M in a 24 month single-arm, OLE (NCT04072575) study (**Figure 1**), were analyzed

FIGURE 1: Overview of the study design



*The initial dose of PP6M in this study was determined based on the dose level ("moderate" or "higher") that the participant received during the double-blind Phase of non-inferiority study. The PP6M dose level were adjusted (700 or 1000 mg eq.) later in the study, based on clinical judgment. †=PP6M injection.
MA, Maintenance; PP3M, paliperidone palmitate 3-month formulation; PP6M, paliperidone palmitate 6-month formulation.

Assessments:

- Improvements over 36 months in a subset of patients with PNS from DB and OLE phases in:
  - Positive and Negative Syndrome Scale (PANSS) for Negative Subscale Score (NSS)
  - Negative Symptoms Factor Score (PANSS NSFS)
  - Factors leading to secondary negative symptoms: Disorganized Thoughts, Uncontrolled Hostility-Excitement, and Anxiety-Depression
  - Personal and Social Performance (PSP)
  - PANSS total score

Definition of PNS subgroup[¶]

PNS was defined as ≥2 PANSS negative symptom items (N1-N4, N6, G7, and G13) rated ≥4 (moderate) and a sum score >20. Participants in the predominant subgroup were required to have PANSS items (P1, P3, P6, P7, and G8) rated <4, and items (P4, P5, G1-G6, G9, G10, and G14) rated <5, with a maximum of 4 items rated as 4

Statistical analysis

- Continuous outcomes were summarized using observed values and change from baseline, with the number of participants (N), mean, standard deviation (SD) or standard error (SE), median, and range reported, as appropriate
- Categorical outcomes (including baseline characteristics) were summarized using counts and percentages
- Outcomes were evaluated at double-blind baseline and at scheduled visits throughout the 36-month treatment period. Within-patient changes from baseline at each time point were evaluated using paired t-tests; p-values and 95% confidence intervals for the mean change were reported
- As this was an exploratory post-hoc analysis, no multiplicity adjustments were applied. Analyses were conducted using observed data without imputation for missing values

Results

Baseline demographic and clinical characteristics

- Of 701 pts from the DB phase, 87 had PNS of which 80 completed the DB phase; 31 pts continued PP6M or switched from PP3M to PP6M in the OLE
- In PNS subgroup, mean (SD) age was 41.6 (11.93) years and 71.3% were male (**Table 1**)

Table 1. Demographics and baseline characteristics of PNS subgroup

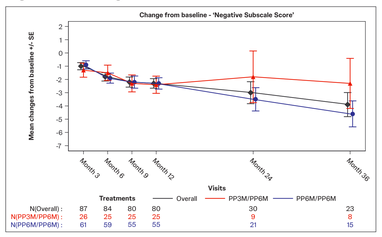
Characteristics	Predominant		
	PP3M (n=26)	PP6M (n=61)	Total (n=87)
Age, mean (SD), years	41.8 (11.28)	41.5 (12.28)	41.6 (11.93)
Sex, n (%)			
Men	17 (65.4)	45 (73.8)	62 (71.3)
Race, n (%)			
Asian	3 (11.5)	7 (11.5)	10 (11.5)
Black or African American	4 (15.4)	2 (3.3)	6 (6.9)
Native Hawaiian or Other Pacific Islander	0	1 (1.6)	1 (1.1)
White	18 (69.2)	51 (83.6)	69 (79.3)
Multiple	1 (3.8)	0	1 (1.1)
Number of prior hosp. psychosis 24 months[a], n (%)			
N	19	45	64
None	12 (63.2)	24 (53.3)	36 (56.3)
One time	6 (31.6)	8 (17.8)	14 (21.9)
Two times	1 (5.3)	8 (17.8)	9 (14.1)
Three times	0	3 (6.7)	3 (4.7)
Four times or more	0	2 (4.4)	2 (3.1)

[a]Number of the most recent hospitalization for psychosis, any time prior to study start (not restricted to 24 months prior to study start). DB, Double-blind; PNS, Predominant negative symptoms; PP3M, Paliperidone palmitate 3-month formulation; PP6M, Paliperidone palmitate 6-month formulation; SD, Standard deviation.

Improvements in PANSS NSS

- Mean (SE) baseline PANSS NSS was 20.8 (0.26; n=86) indicating moderate to severe level of negative impairment in enrolled patients
- The PANSS NSS showed improvements throughout the 12 months DB study and further improved through 36 months in OLE study (**Figure 2**)
  - PANSS NSS at 12 months: (18.4 [0.43]; n=80), mean (SE) change from baseline (CFB) was −2.3 (0.36; 95% CI: −3.03, −1.60; p<0.001)
  - PANSS NSS at 36 months: (16.3 [0.84]; n=23), mean [SE] CFB was −3.9 (0.91; 95% CI: −5.75, −1.98; p<0.001)
- Median (range) CFB in PANSS NSS were −2.0 (−10, 6) at 12 months and −5.0 (−11, 7) at 36 months
- Both PP3M and PP6M groups demonstrated early improvements in 12 months, improvement in NSS continued after month 12 to month 36 with PP6M (**Figure 2**)

Figure 2: Changes in PANSS NSS

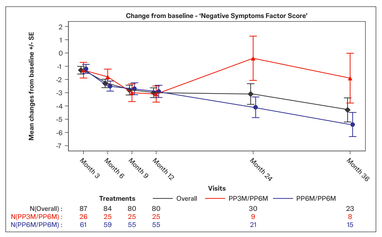


NSS, Negative subscale score; PANSS, Positive and Negative Syndrome Scale; PP3M, Paliperidone palmitate 3-month formulation; PP6M, Paliperidone palmitate 6-month formulation; SE, Standard error.

Improvements in PANSS NSFS

- Mean (standard error [SE]) baseline PANSS NSFS was 19.7 (0.25; n=86)
- The PANSS NSFS showed improvements throughout the 12-months DB study and was maintained through 36 months in OLE study (**Figure 3**)
  - PANSS NSFS at 12 months: 16.7 (0.40, n=80); mean (SE) CFB: −3.0 (0.37; 95% CI: −3.70, −2.23; p<0.001)
  - PANSS NSFS at 36 months: 15.1 (0.83; n=23); mean (SE) CFB: −4.3 (0.91; 95% CI: −6.16, −2.38; p<0.001)
- Median (range) CFB in PANSS NSFS were −2.0 (−11, 6) at 12 months and −5.0 (−12, 7) at 36 months
- Both PP3M and PP6M groups demonstrated gradual reductions in 12 months, improvement in NSFS continued after month 12 to month 36 with PP6M (**Figure 3**)

Figure 3: Changes in secondary NSFS



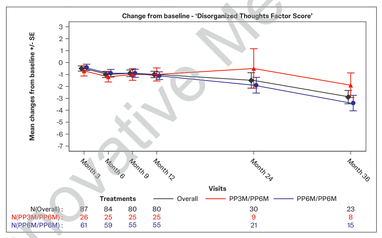
PP3M, Paliperidone palmitate 3-month formulation; PP6M, Paliperidone palmitate 6-month formulation; SE, Standard error

Changes in factors leading to secondary negative symptoms

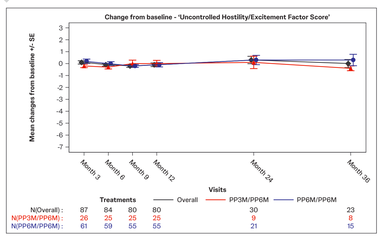
- Mean (SE) CFB to 36 months (n=23) in these factors were stable or minimal (**Figure 4**) for
  - Disorganized Thoughts: (−2.9 [0.56; 95% CI: −4.08, −1.74; p<0.001], from baseline of 15.2 [0.34])
  - Uncontrolled Hostility-Excitement: (0.0 [0.34; 95% CI: −0.66, 0.75; p=0.894], from baseline of 4.7 [0.10])
  - Anxiety-Depression: (−0.9 [0.50; 95% CI: −1.96, 0.14; p=0.086], from baseline of 5.4 [0.19])
- Improvement in Disorganized Thoughts continued after month 12 to month 36 with PP6M (**Figure 4**)

Figure 4: Changes in factors leading to secondary negative symptoms

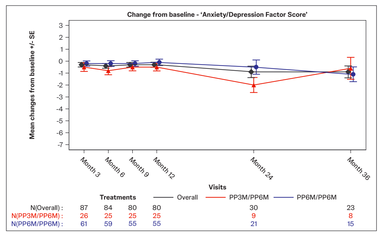
a) Disorganized Thoughts Factor Score



b) Uncontrolled Hostility/Excitement Factors Score



c) Anxiety/Depression Factor Score



PP3M, Paliperidone palmitate 3-month formulation; PP6M, Paliperidone palmitate 6-month formulation; SNS, Secondary negative symptoms; SE, Standard error.

Functional improvements

- The functional improvements in PANSS total score and PSP total score were observed through 12 months and then further improved through 36 months (**Table 2**)

Table 2: Functional improvements

	N	Mean (SE)	Mean (SE) CFB, 95% CI (p-value)	Median (range) CFB
PANSS total score				
Baseline	86	58.5 (0.68)	-	-
12 months	80	53.1 (0.99)	−5.0 (0.76), 95% CI (−6.54, −3.51), p<0.001	−4.0 (−22, 13)
36 months	23	49.3 (2.01)	−9.5 (1.76), 95% CI (−13.21, −5.88), p<0.001	−12.5 (−21, 6)
PSP total score				
Baseline	87	59.0 (1.18)	-	-
12 months	80	64.0 (1.27)	4.9 (0.84), 95% CI (3.18, 6.52), p<0.001	4.0 (−9, 27)
36 months	24	76.0 (1.64)	10.5 (2.09), 95% CI (6.21, 14.87), p<0.001	10.5 (−5, 33)

CI, Confidence interval; CFB, Change from baseline; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; SE, Standard deviation.

Study limitations

- Exploratory post-hoc analysis; findings are descriptive, not confirmatory
- OLE phase was single-arm, with no concurrent control group
- Only 12.4% of the patients met criteria for predominant negative symptoms, limiting PP3M vs PP6M comparisons
- Low number of patients in the OLE further constrained interpretability

Conclusion

- In patients with predominant negative symptoms (PNS), PP6M was associated with sustained improvements in PANSS negative symptom measures (PANSS NSS and PANSS NSFS) over 1–3 years
- Improvements in negative symptoms were accompanied by meaningful enhancements in personal and social functioning, as reflected by PSP score and PANSS total score
- Overall, PP6M demonstrated consistent and clinically meaningful long-term benefits on negative symptoms and functioning in patients with schizophrenia and PNS

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Disclosures

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