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BRIEF REPORT

Paliperidone palmitate once-every-3-months in adults with early illness schizophrenia

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Aim: This post hoc analysis of a double-blind (DB), randomized, placebo-controlled, relapse-prevention study evaluated the effects of paliperidone palmitate once-every-3-months (PP3M) in a subpopulation of adults with early illness schizophrenia (duration ≤5 years) from a clinical trial.

Methods: Patients received either PP3M or placebo every 3 months in the DB phase. The primary efficacy variable was time from randomization to first relapse. Symptom severity, patient functioning, and safety were also assessed.

Results: A total of 119 patients who entered the DB phase met the criteria for early illness schizophrenia (PP3M, n = 62; placebo, n = 57). PP3M significantly delayed time to relapse vs placebo (P = .035; hazard ratio, 3.08; 95% CI, 1.08-8.80). Symptomatic control and patient functioning were maintained in the PP3M group but significantly worsened in the placebo group. There were no unexpected tolerability findings.

Conclusions: PP3M reduced relapse risk and maintained symptomatic and functional improvements compared with placebo in patients with early illness schizophrenia.

KEYWORDS

early illness, paliperidone palmitate, recently diagnosed, relapse, schizophrenia

1 | INTRODUCTION

In persons with schizophrenia, the first 5 years following the initial psychotic episode is a critical period for effective intervention (Emsley, Chiliza, & Asmal, 2013; McGorry, 2005). A growing body of evidence indicates that relapse events may cause adverse brain changes and that treatment response tends to diminish with each successive relapse (Emsley et al., 2013; Jeong & Lee, 2013; Lieberman, 2006). Therefore, sustained symptom control through consistent antipsychotic treatment during the early phase of schizophrenia is an important factor in maintaining patient functioning (Lehman et al., 2004). Incomplete adherence to antipsychotic medications is common among patients with schizophrenia, leading to an increased risk of relapse and hospitalization (Correll et al., 2016; Lang et al., 2010; Panish, Karve, Candrilli, & Dirani, 2013). This may be even more common among patients with early illness due to various factors, including lack of social support, negative attitude toward medication, and poor insight (Acosta, Hernandez, Pereira, Herrera, & Rodriguez, 2012;

Ceskova, Prikryl, Kasparek, & Ondrusova, 2005; Heres, Lambert, & Vauth, 2014; Quach et al., 2009).

Long-acting injectable (LAI) formulations of antipsychotic medications provide therapeutic plasma concentrations that are sustained for weeks to months following administration, eliminating the need for daily adherence to oral antipsychotics (Correll et al., 2016; Spanarello & La Ferla, 2014). Paliperidone palmitate once-every-3-months (PP3M) is approved for the treatment of adult patients with schizophrenia who have been adequately treated with paliperidone palmitate once-monthly (PP1M) for ≥4 months (Janssen Pharmaceuticals Inc, 2017). The results of a multicentre, double-blind (DB), randomized, placebo-controlled study showed that PP3M significantly delayed time to relapse compared with placebo in patients adequately treated with PP1M (Berwaerts et al., 2015). Several studies have reported on the feasibility and benefit of LAIs for the treatment of patients with early illness schizophrenia (Alphs, Bossie, Mao, Lee, & Starr, 2015; Schreiner et al., 2015; Subotnik et al., 2015; Weiden et al., 2009), but the effects of PP3M on early illness have not been

investigated. This post hoc analysis examines the efficacy and safety of PP3M in a subpopulation of patients diagnosed with schizophrenia ≤5 years before trial enrolment.

2 | METHODS

Details of this study are described elsewhere (ClinicalTrials.gov identifier, NCT01529515) (Berwaerts et al., 2015). Men and women (aged 18-70 years) with schizophrenia (DSM-IV-TR criteria) for ≥1 year before screening who had a Positive and Negative Syndrome Scale (PANSS) total score of <120 at screening were eligible for study participation. Patients were excluded from the study if they had an active DSM-IV axis diagnosis other than schizophrenia or involuntary status in a psychiatric hospital at screening. An independent ethics committee or institutional review board approved the study protocol and amendments at each site. All studies were conducted in compliance with the Declaration of Helsinki and were consistent with Good Clinical Practice and applicable regulatory requirements. All patients provided written informed consent before enrolment. For the present analysis, patients diagnosed with schizophrenia ≤5 years before trial enrolment were considered to have early illness.

This relapse-prevention, DB, randomized, placebo-controlled, multi-centre study consisted of 4 phases: a 3-week screening phase; a flexible-dose, 17-week, open-label (OL) transitional phase; a 12-week OL maintenance phase; and a variable follow-up DB phase. Patients received PP1M (78, 117, 156, or 234 mg) during the transition phase, followed by a single dose of PP3M (3.5 times the stabilized dose of PP1M) during the maintenance phase. Stabilized patients were randomized to either the same fixed dose of PP3M or placebo every 3 months during the DB phase.

For this post hoc analysis, the primary efficacy variable was time from randomization to first relapse event in the DB phase. Secondary efficacy variables were change from DB baseline to endpoint in PANSS total score; PANSS positive, negative, and general psychopathology subscale scores; Clinical Global Impression of Severity (CGI-S) scale score; and Personal and Social Performance (PSP) scale total score. Safety assessments included evaluation of treatment-emergent adverse events (TEAEs).

The DB intention-to-treat final analysis set was defined as all those who were randomized and received ≥1 dose of study drug in the DB phase. The safety analysis set was identical to the DB intention-to-treat analysis set. Kaplan-Meier method was used to assess time to relapse, and the log-rank test was used to compare treatment differences. Risk of relapse between the treatment groups was examined using the Cox proportional hazards model. Treatment comparisons between PP3M and placebo in changes from baseline to DB endpoint of PANSS total, PANSS subscale, CGI-S, and PSP total scores were performed using an ANCOVA model with fixed effects for treatment, country, and baseline values as covariates. Changes from baseline within treatment groups were examined using paired t-test.

3 | RESULTS

Of the 620 screened patients, 506 entered the OL phase. A total of 305 patients who met protocol-defined stabilization criteria at the end of the OL phase entered the DB phase; 160 of these patients were randomized to PP3M (n = 62 [38.8%] with early illness) and 145 were randomized to placebo (n = 57 [39.3%] with early illness). Demographic and disease characteristics for the early illness population were well balanced between treatment groups (Table 1).

Among those with early illness, 12 (21.1%) patients in the placebo group and 5 (8.1%) patients in the PP3M group experienced relapse during the DB phase (Figure 1). Median time to relapse could not be computed because less than 50% of patients relapsed in each treatment group. Continued treatment with PP3M was associated with a significant delay in time to relapse compared with placebo (P = .027) using the log-rank test. In addition to the Kaplan-Meier analysis, the estimate of the hazard ratio (risk) and its 95% CI was provided based on the Cox proportional hazards model. The risk of relapse (hazard

TABLE 1 Baseline demographic and disease characteristics for patients in the double-blind phase with duration of illness ≤5 years

Parameter	Double-blind phase	
	Placebo n = 57	PP3M n = 62
Age, years		
Mean (SD)	31.8 (9.71)	31.2 (9.59)
Median (min, max)	29.0 (18, 53)	29.0 (18, 60)
Age category, years, n (%)		
18-25	19 (33.3)	22 (35.5)
26-30	10 (17.5)	11 (17.7)
31-35	10 (17.5)	17 (27.4)
>35	18 (31.6)	12 (19.4)
Gender, n (%)		
Male	46 (80.7)	40 (64.5)
Race, n (%)		
White	37 (64.9)	47 (75.8)
Black or African American	7 (12.3)	5 (8.1)
Asian	6 (10.5)	3 (4.8)
Other	7 (12.3)	7 (11.3)
Ethnicity, n (%)		
Hispanic or Latino	12 (21.1)	12 (19.4)
Not Hispanic or Latino	44 (77.2)	50 (80.6)
Not reported/Unknown	1 (1.8)	0 (0.0)
Country, n (%)		
Colombia	7 (12.3)	9 (14.5)
Malaysia	5 (8.8)	2 (3.3)
Mexico	4 (7.0)	0 (0.0)
Romania	2 (3.5)	4 (6.5)
South Korea	1 (1.8)	1 (1.6)
Turkey	4 (7.0)	2 (3.2)
Ukraine	27 (47.4)	36 (58.1)
United States	7 (12.3)	8 (12.9)
Body weight, kg		
Mean (SD)	77.1 (14.8)	75.0 (14.1)
Median (min, max)	75.2 (44, 120)	73.2 (47, 118)
BMI (kg/m^2)		
Mean (SD)	25.9 (4.2)	25.4 (4.6)
Median (min, max)	25.2 (18, 37)	24.4 (18, 40)

Abbreviations: BMI, body mass index; max, maximum; min, minimum; PP3M, paliperidone palmitate once-every-3-months; SD, standard deviation.
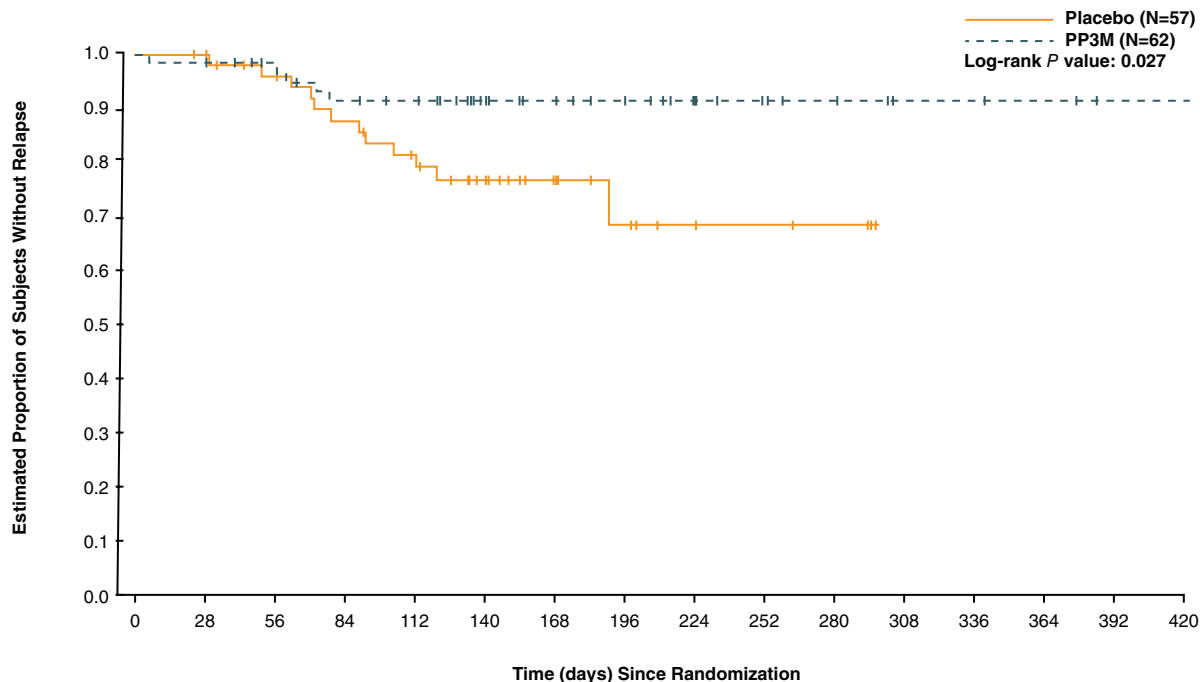
FIGURE 1 Kaplan-Meier plot of time to relapse during the double-blind (DB) phase in patients with early illness: intention-to-treat (DB) analysis set. Paliperidone palmitate once-every-3-months (PP3M) significantly delayed time to relapse versus placebo (P = .035; hazard ratio, 3.08; 95% CI, 1.08, 8.80)

ratio) was 3.08-fold higher (95% CI: 1.08, 8.80; P = .035) for patients randomized to placebo after a single dose of PP3M than for those who continued to receive PP3M in the DB phase.

Mean changes from DB baseline to DB endpoint in PANSS total and subscale, CGI-S, and PSP total scores for patients in the placebo and PP3M groups are shown in Table 2. At the end of the DB phase, scores were maintained in the PP3M group. Mean [SD] changes from DB baseline were PANSS total (−0.3 [7.9]; P = .783), PANSS positive subscale (0.4 [2.6]; P = .224), PANSS negative subscale (−0.2 [2.9]; P = .511), PANSS general psychopathology subscale (−0.4 [4.5]; P = .445), CGI-S (0.1 [0.60]; P = .398), and PSP total (−0.4 [7.2]; P = .660) scores. However, with the exception of the PANSS negative subscale, the scores significantly worsened in the placebo group: PANSS total (5.9 [15.3]; P = .006), PANSS positive subscale (2.5 [5.3]; P = .001), PANSS negative subscale (0.8 [3.8]; P = .115), PANSS general psychopathology subscale (2.6 [8.3]; P = .023), CGI-S (0.3 [0.86]; P = .021), and PSP total (−3.5 [10.3]; P = .016) scores. A significant between-group difference in favour of PP3M was demonstrated for PANSS total, positive, negative, and general psychopathology subscale; CGI-S; and PSP total scores: the LS mean (95% CI) difference in change between the 2 treatment groups were 7.1 (2.5, 11.7; P = .003), 2.1 (0.5, 3.7; P = .011), 1.5 (0.2, 2.7; P = .019), 3.6 (1.0, 6.1; P = .006), 0.3 (0.0, 0.6; P = .025), and −3.8 (−7.2, −0.4; P = .031), respectively.

Among patients with early illness, the most common TEAEs (≥2%) occurring more frequently in the PP3M group than in the placebo group during the DB phase were weight increased (12.9% vs 3.5%), anxiety (9.7% vs 8.8%), nasopharyngitis (8.1% vs 3.5%), headache

(8.1% vs 1.8%), urinary tract infection (6.5% vs 0.0%), and akathisia (3.2% vs 0.0%), respectively (Table 3). In the DB phase, 3 serious adverse events were experienced by 8 patients: paranoid-type schizophrenia (n = 1) in the PP3M group and schizophrenia (n = 6) and cellulitis (n = 1) in the placebo group. There were no deaths during the DB phase and no patient withdrew due to a TEAE.

4 | DISCUSSION

This post hoc analysis demonstrates the efficacy and safety of PP3M in a subpopulation of patients with early illness schizophrenia and is consistent with the primary results of the trial (Berwaerts et al., 2015). Specifically, the use of PP3M significantly delayed time to relapse compared with placebo, and PP3M maintained both symptomatic and functional status in early illness patients. Conversely, symptom severity and patient functioning worsened in patients randomized to placebo. There were no unexpected tolerability findings in patients with early illness.

Patients with early illness schizophrenia are often nonadherent to antipsychotic medications due to poor awareness and knowledge of their illness and the importance of continuous, effective medication therapy (Ceskova et al., 2005; Quach et al., 2009). This population is therefore particularly vulnerable to relapse, with the potential for irreversible cognitive deterioration (Nuechterlein, Ventura, Subotnik, & Bartzokis, 2014). Psychiatrists may be reluctant to treat early episode schizophrenia with LAIs (Altamura et al., 2012; Correll et al., 2016; Jeong & Lee, 2013). However, patients with first-episode

TABLE 2 Change from baseline to endpoint in Positive and Negative Syndrome Scale, Clinical Global Impression of Severity scale, and Personal and Social Performance scale scores for patients in the double-blind phase with duration of illness ≤5 years

Parameter	Placebo n = 54	PP3M n = 61	Estimate[a]
Double-blind phase			
PANSS scores			
Total score			
Baseline, mean (SD)	54.0 (9.7)	54.9 (10.9)	
Endpoint, mean (SD)	60.0 (18.3)	54.6 (13.2)	
Change from baseline, mean (SD)	5.9 (15.3)	−0.3 (7.9)	
P value[b]	.006	.783	
Change from baseline, LS mean (SE)	5.2 (2.1)	−1.9 (2.2)	
LS mean difference (95% CI)			7.1 (2.5, 11.7)
P value			.003
Positive subscale score			
Baseline, mean (SD)	11.4 (3.1)	11.4 (3.3)	
Endpoint, mean (SD)	13.9 (6.2)	11.8 (4.1)	
Change from baseline, mean (SD)	2.5 (5.3)	0.4 (2.6)	
P value[b]	.001	.224	
Change from baseline, LS mean (SE)	2.7 (0.7)	0.6 (0.8)	
LS mean difference (95% CI)			2.1 (0.5, 3.7)
P value			.011
Negative subscale score			
Baseline, mean (SD)	16.1 (4.0)	16.4 (4.8)	
Endpoint, mean (SD)	16.9 (5.2)	16.2 (5.0)	
Change from baseline, mean (SD)	0.8 (3.8)	−0.2 (2.9)	
P value[b]	.115	.511	
Change from baseline, LS mean (SE)	0.1 (0.6)	−1.4 (0.6)	
LS mean difference (95% CI)			1.5 (0.2, 2.7)
P value			.019
General psychopathology subscale score			
Baseline, mean (SD)	26.6 (4.9)	27.0 (5.1)	
Endpoint, mean (SD)	29.2 (9.6)	26.6 (6.4)	
Change from baseline, mean (SD)	2.6 (8.3)	−0.4 (4.5)	
P value[b]	.023	.445	
Change from baseline, LS mean (SE)	2.4 (1.2)	−1.2 (1.2)	
LS mean difference (95% CI)			3.6 (1.0, 6.1)
P value			.006
CGI-S scale score			
Baseline, mean (SD)	2.8 (0.70)	2.8 (0.62)	
Endpoint, mean (SD)	3.1 (1.00)	2.8 (0.88)	
Change from baseline, mean (SD)	0.3 (0.86)	0.1 (0.60)	
P value[b]	.021	.398	
Change from baseline, LS mean (SE)	0.2 (0.12)	−0.1 (0.13)	

TABLE 2 (Continued)

Parameter	Placebo n = 54	PP3M n = 61	Estimate[a]
Double-blind phase			
LS mean difference (95% CI)			0.3 (0.0, 0.6)
P value			.025
PSP total score			
Baseline, mean (SD)	68.1 (9.1)	69.7 (8.7)	
Endpoint, mean (SD)	64.6 (12.7)	69.2 (11.8)	
Change from baseline, mean (SD)	−3.5 (10.3)	−0.4 (7.2)	
P value[b]	.016	.660	
Change from baseline, LS mean (SE)	−3.8 (1.6)	−0.1 (1.6)	
LS mean difference (95% CI)			−3.8 (−7.2, −0.4)
P value			.031

Abbreviations: CGI-S, Clinical Global Impression of Severity; PANSS, Positive and Negative Symptom Scale; PP3M, paliperidone palmitate once-every-3-months; PSP, Personal and Social Performance; SD, standard deviation.

[a] P values for between-group comparisons are from an analysis of covariance model with fixed effects for treatment and country and the baseline value as a covariate.

[b] P values for within-group comparisons are based on a paired t - test.

schizophrenia may be surprisingly open to LAI treatment after stabilization on oral antipsychotic medication (Weiden et al., 2009). Given the high prevalence of nonadherence to oral medications and the potential negative consequences of relapses in this population, clinician reluctance to offer LAIs to patients with early episode schizophrenia is not supported by available evidence (Weiden et al., 2009). The findings presented here are also consistent with findings from studies of patients with early illness receiving PP1M (Alphs et al.,

TABLE 3 Most common treatment-emergent adverse events (≥2% in either treatment group during the double-blind phase)

Parameter	Placebo n = 57	PP3M n = 62
Double-blind phase		
Patients with AEs, n (%)	28 (50.9)	39 (62.9)
Weight increased	2 (3.5)	8 (12.9)
Anxiety	5 (8.8)	6 (9.7)
Headache	1 (1.8)	5 (8.1)
Nasopharyngitis	2 (3.5)	5 (8.1)
Insomnia	9 (15.8)	4 (6.5)
Urinary tract infection	0 (0.0)	4 (6.5)
Akathisia	0 (0.0)	2 (3.2)
Influenza	3 (5.3)	1 (1.6)
Schizophrenia	8 (14.0)	1 (1.6)
Weight decreased	2 (3.5)	1 (1.6)
Dyskinesia	2 (3.5)	0 (0.0)
Cough	2 (3.5)	0 (0.0)
Hyperglycaemia	2 (3.5)	0 (0.0)

Abbreviations: AEs, adverse events; PP3M, paliperidone palmitate once-every-3-months.

2015; Bossie, Fu, Sliwa, Ma, & Alphs, 2011; Fu, Bossie, Sliwa, Ma, & Alphs, 2014; Schreiner et al., 2015). Additionally, the Canadian Schizophrenia Guidelines acknowledge that use of LAIs earlier in the course of treatment has been advocated and that discussions regarding LAI use should not be limited to patients with poor adherence (Remington et al., 2017).

This post hoc analysis has several limitations. First, the study was not designed to evaluate the efficacy and safety of PP3M in patients with early illness. Second, the present analysis used a 5-year cutoff to define early illness; however, there is no consensus on the definition of "early illness" and it can be defined in several ways (Canuso et al., 2010; Dubois, Peuskens, Geerts, & Detraux, 2014; Kreyenbuhl et al., 2016; Macfadden, Bossie, Turkoz, & Haskins, 2010). Finally, this was an international study, and the duration of illness as reported by the investigators may be influenced by local cultural norms that could accelerate or delay the receipt of an appropriate diagnosis following symptom onset (Berwaerts et al., 2015).

In conclusion, results of this post hoc analysis demonstrate that in adults with ≤5 years' duration of schizophrenia, PP3M is efficacious and tolerated; these findings are consistent with the primary analysis. Use in this population could help patients maintain sustained symptom control during a critical period when relapses can be disruptive yet potentially avoidable.

Author disclosures

K.S.B.L. and E.K. are employees of Janssen Scientific Affairs, LLC, and are stockholders of Johnson & Johnson. I.T. is an employee of Janssen Research & Development, LLC, and is a stockholder of Johnson & Johnson.

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