



## ORIGINAL RESEARCH

# Paliperidone Palmitate Improves and Maintains Functioning in Asia–Pacific Patients with Schizophrenia

Hongyan Zhang · Ibrahim Turkoz · Jianmin Zhuo · Maju Mathews ·  
Wilson Tan · Yu Feng

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## ABSTRACT

**Introduction:** Post hoc analyses (two single-arm studies) were conducted to determine the impact of once-monthly injection of paliperidone palmitate on functioning in adult patients with schizophrenia in the Asia–Pacific region.

**Methods:** Study 1 enrolled hospitalized patients with acute exacerbation of schizophrenia, and study 2 enrolled patients with recently diagnosed schizophrenia unsatisfactorily treated with oral antipsychotics.

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H. Zhang  
Peking University Sixth Hospital, Peking University  
Institute of Mental Health, Key Laboratory of  
Mental Health, Ministry of Health (Peking  
University), Beijing, China

I. Turkoz · M. Mathews  
Janssen Research & Development LLC, Titusville,  
NJ, USA

J. Zhuo  
Janssen China Research & Development Center,  
Johnson & Johnson (China) Investment Ltd,  
Shanghai, China

W. Tan · Y. Feng (✉)  
Janssen Pharmaceutical Companies of Johnson &  
Johnson, Singapore, Singapore  
e-mail: yfeng23@ITS.JNJ.COM

Patients received paliperidone palmitate, 150 mg eq. on day 1, 100 mg eq. on day 8, then once monthly (50–150 mg eq.) (study 1, days 36 and 64; study 2, 18 months). Functional status was evaluated by Personal and Social Performance score in both studies and employment only in study 2.

**Results:** In study 1, 54 of 184 patients (29.4%) with an unfavorable level of functioning at the baseline improved to a favorable level (Personal and Social Performance score greater than 70) at day 92. This improvement was significantly greater among patients with recently diagnosed schizophrenia (5 years or less) compared with patients with chronic schizophrenia (more than 5 years): 40% versus 22% ( $p < 0.0001$ ). Improvements were observed in all four domains (socially useful activities, personal and social relationships, self-care, disturbing/aggressive behavior). In study 2, significant ( $p < 0.0001$ ) improvement in functioning was observed at all visits, beginning at week 5. Almost half (48.7%, 247/507) of patients showed clinically meaningful improvement in functioning (i.e., 10 point or greater increase in Personal and Social Performance score) at month 18. The proportion of patients fully/partially employed was greater at all post-baseline visits (134 of 280, 47.9%, at month 18) as compared with the baseline.

**Conclusion:** Functioning, including employment, was improved after short-term, once-monthly paliperidone palmitate injection, and

was sustained to 18 months in Asia–Pacific patients with schizophrenia.

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**Keywords:** Functioning; Long-acting injectables; Paliperidone palmitate; Schizophrenia

## INTRODUCTION

Schizophrenia is a chronic mental illness characterized by a range of severe psychotic symptoms that may recur and progress over time [1, 2], adversely affecting the lives of patients and their caregivers [3, 4]. Furthermore, deficits in social functioning are a core feature of schizophrenia; therefore, not surprisingly, deterioration (or failure to achieve adequate levels) of social functioning is a diagnostic criterion of schizophrenia [5]. In addition to social functioning, occupational aspects of patient functioning may also be affected, as is independent living [6, 7].

Functional disability is recognized as an important long-term outcome of patients with schizophrenia [8, 9]. Most patients (up to two thirds) cannot perform basic social roles, even during periods of remission, few marry, and only a minority (less than one third) are able to maintain everyday employment [10]. According to Rosenheck et al. [11], only one in every seven patients with schizophrenia reported regular, paid employment, and those who were unemployed reported lower quality-of-life scores. Social dysfunction is an important aspect in the overall disability of schizophrenia, causing great distress for not only patients but also their family [10]. Taken together, the societal (including economic) burden of poor functioning among those with schizophrenia is sizable [10].

Beyond control of characteristic positive and negative symptoms and delaying/prevention of recurrence, functional recovery is also a requisite goal of schizophrenia treatment and an important determinant of treatment success [12–14]. Affected patients as well as their families acknowledge the importance of improved functioning among their expectations for

treatment [10], which is therefore included in schizophrenia treatment guidelines [4, 15, 16]. However, evidence of the effect of antipsychotic agents on social and occupational functioning in schizophrenia patients, especially those in the Asia–Pacific region, is limited.

Paliperidone palmitate 1-month formulation (PP1M), a once-monthly long-acting injectable (LAI) atypical antipsychotic, is approved in the USA, Europe, and major Asia–Pacific countries for acute and maintenance treatment of schizophrenia. Proof of its efficacy and safety for treatment of schizophrenia was established on the basis of results of numerous studies conducted across these geographic regions [17–34], including the Asia–Pacific region [35–40]. Improvement in function among PP1M-treated patients as assessed by the Personal and Social Performance (PSP) scale [41], a validated, clinician-reported instrument for assessing personal and social functioning of patients with schizophrenia [42], was reported in several global studies [17–19, 22, 24–26, 28–33] and in Asia–Pacific regional studies [35–38].

In clinical practice, many physicians use an LAI as the last choice rather than the first choice. Given the importance of personal, social, and occupational functioning and the aim of improving outcomes of schizophrenia patients, additional PSP analyses were conducted to examine the effect of PP1M on the various dimensions of functioning in patients with schizophrenia across the Asia–Pacific region. Further analyses were performed to evaluate the effects of PP1M in patients with recently diagnosed schizophrenia (5 years or less) as compared with chronic disease (more than 5 years). The results for Positive and Negative Syndrome Scale (PANSS) total score, the primary efficacy end point, and other pre-specified secondary end points (e.g., PANSS domain/symptom factor scores, Clinical Global Impression–Schizophrenia, Clinical Global Impression–Severity, symptom remission) of the studies are reported elsewhere [36, 40].

## METHODS

An independent ethics committee or institutional review board at the study sites approved

the study protocol of each study, and both studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable regulatory requirements. All patients or their legally acceptable representatives provided written informed consent before the patients entered one of the studies. Study 1 [36] (NCT01527305) and study 2 [40] (NCT01051531) are registered at ClinicalTrials.gov.

## Study 1

### *Patients*

Asian patients of either sex, between 18 and 65 years old, with a diagnosis of schizophrenia (based on *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), criteria [43]), with a PANSS total score of 60 or greater or a Clinical Global Impression–Severity score of 4 or greater, and hospitalized with an acute exacerbation within the previous 4 weeks were enrolled. Those with a primary active DSM-IV Axis I diagnosis other than schizophrenia, a history of substance dependence within 6 months of screening, at significant suicide risk, and who used clozapine or long-acting antipsychotics (including PP1M) within 1 month of screening were excluded.

### *Study Design and Treatment*

This nonrandomized, single-arm, open-label, multicenter study was conducted between June 2012 and December 2013 across four Asian countries including China (six sites), Korea (ten sites), Malaysia (three sites), and Taiwan (eight sites). The study consisted of an up to 7-day screening period, followed by an open-label treatment period (13 weeks), and an end-of-study visit on day 92 (week 13), 1 month after the last PP1M injection.

On day 1, eligible patients were switched to treatment with PP1M from their existing oral antipsychotic medication. Patients without documented tolerability to orally administered risperidone, extended-release paliperidone, risperidone LAI, or PP1M underwent oral tolerability testing during the screening period with

extended-release paliperidone, 3 mg/day, or orally administered risperidone, 1 mg/day, for at least 2 days. Treatment with PP1M was initiated at a dose of 150 mg eq. on day 1, followed by 100 mg eq. on day 8 (both doses in the deltoid muscle) and flexible once-monthly injections of 75, 100, or 150 mg eq. in the deltoid or gluteal muscle, at the investigator's discretion, on days 36 and 64.

### *Assessment of Functioning*

Functional status was evaluated by PSP, which was administered to patients by a trained and qualified clinician/rater at the baseline and at visits conducted on days 4, 8, 36, 64, and 92.

PSP is a clinician-rated instrument that provides an overall rating of personal and social functioning in patients with schizophrenia [41]. The scale, which ranges from 1 to 100, defines a continuum of functioning from grossly impaired, in which total lack of autonomy in basic functioning and survival risk is evident, to excellent functioning. Higher scores represent better functioning. Four domains of functioning are considered in the rating: (1) socially useful activities, including work and study; (2) personal and social relationships; (3) self-care; and (4) disturbing and aggressive behavior. For each domain, the degree of dysfunction a patient exhibits during the month before a visit is rated on a six-point severity scale (absent, mild, manifest, marked, severe, and very severe).

## Study 2

### *Patients*

Adults (between 18 and 50 years old) with a recent (5 years or less) diagnosis of schizophrenia (based on DSM-IV criteria [43]) who had not responded adequately to previous oral antipsychotics (because of lack of efficacy, tolerability/safety, or adherence) were enrolled. Key exclusion criteria were as follows: treatment resistance; DSM-IV diagnosis of substance dependence in the 6 months before entry to the study; treatment with an LAI antipsychotic within three injection cycles before the baseline or clozapine within the most recent prior 3 months.

### **Study Design and Treatment**

This 18-month, nonrandomized, single-arm, open-label, multicenter study was conducted between April 2010 and May 2013 across nine countries in the Asia–Pacific region, including Australia (nine sites), China (six sites), Hong Kong (two sites), Korea (ten sites), Malaysia (nine sites), New Zealand (one site), Philippines (two sites), Taiwan (six sites), and Thailand (three sites). The study consisted of an up to 7-day screening period, followed by an 18-month open-label treatment period, and an end-of-study/early-withdrawal visit 1 month after the last PP1M injection.

Eligible patients were switched to treatment with PP1M from their existing oral antipsychotic treatment that was discontinued before day 1, with the exception that those pretreated with high doses of oral antipsychotics having sedating and/or anticholinergic properties could taper off these medications through the first month of the study. Treatment with PP1M was initiated at a dose of 150 mg eq. on day 1, followed by 100 mg eq. on day 8 (both doses in the deltoid muscle) and flexible once-monthly injections of 50, 75, 100, or 150 mg eq. in the deltoid or gluteal muscle, at the investigator's discretion.

### **Assessments of Functioning and Employment**

In a manner similar to that in study 1, functional status was evaluated by PSP, which a trained and qualified clinician/rater administered to patients at the baseline and at visits conducted on days 38, 188, 368, and 548 (or at early withdrawal) in study 2.

Specifically for study 2, employment status (full-time, part-time, casual, sheltered, unemployed but seeking or not seeking work, retired, housewife or dependent spouse, student) was recorded at every 3-month visits during the 18-month study.

### **Statistical Analyses**

Analyses were performed on an intent-to-treat population, which included all patients who received at least one injection of PP1M. For

efficacy, the last observation carried forward approach was used for end point analyses.

In study 1, baseline demographic and clinical characteristics of patients with recently diagnosed schizophrenia (5 years or less) were compared with those of patients with chronic disease (more than 5 years) by analysis of variance or chi-square tests. The breakpoint of 5 years, differentiating recently diagnosed schizophrenia from chronic schizophrenia, was based on findings from recently published schizophrenia research [44, 45].

The mean change from the baseline in PSP total score to each visit was analyzed with a paired *t* test and two-sided 95% confidence intervals in both studies. In study 1, the mean change in PSP total score between the duration of schizophrenia (5 years or less and more than 5 years) was compared with an analysis of covariance (ANCOVA) model with group as a factor and baseline score as a covariate.

Between-group differences for the categorical summaries of PSP total score (and PSP domain scores in study 1) were compared by a chi-square test (or Fisher's test when cell counts were less than 5), as was clinically meaningful improvement defined by improvement of one or more categories (classified as a 10-point interval) [46, 47]. Shifts from the baseline to each visit by PSP total score category (unfavorable level 70 or less; favorable level more than 70) were summarized, and the change was analyzed at each postbaseline assessment with McNemar's test. In study 2, the shift from the baseline to month 18 in employment status (full employment, partial employment, unemployment, and out of employment) was analyzed by the Bowker (chi-square) test of symmetry.

## **RESULTS**

### **Study 1**

#### **Patient Disposition and Clinical Characteristics**

Study 1 enrolled 212 patients, 152 (71.7%) of whom completed the 13-week treatment. The study population comprised all Asian patients,

and was balanced by sex (Table 1). The mean age was approximately 37 years. With few exceptions, study patients had functional disability at study enrolment (75.5% with varying functioning and 23.6% with a poor level of function that required intensive supervision).

**Change in Functioning with PP1M Treatment**

Significant and clinically meaningful improvement in personal and social functioning from the baseline was observed for PP1M-treated patients. Significantly greater benefit for the mean change in PSP total score at week 13 from

the baseline was observed in patients with recently diagnosed (5 years or less) compared with chronic (more than 5 years) schizophrenia [difference between subgroups with 95% confidence interval of 10.4 (6.14–14.73);  $p < 0.0001$ , Table 2]. In this study, 78.7% of patients (59/75) with recent-onset schizophrenia (5 years or less) and 57.8% or patients (63/109) with chronic schizophrenia (5 years or more) ( $p = 0.033$  for difference between subgroups) showed clinically meaningful improvement in functioning (i.e., 10 point or greater increase in PSP total score).

**Table 1** Baseline demographics and clinical characteristics

Parameter	Study 1		All patients (N = 212)	Study 2 All patients (N = 516)
	Duration of schizophrenia			
	≤ 5 years (N = 88)	> 5 years (N = 124)		
Age (years) <sup>a</sup>	34.2 (12.87)	39.2* (10.60)	37.1 (11.82)	28.7 (7.92)
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	23.0 (4.39) <sup>b</sup>	23.9 (4.12)	23.6 (4.24) <sup>c</sup>	24.4 (5.14)
Sex				
Male	45 (51.1%)	63 (50.8%)	108 (50.9%)	339 (65.6%)
Female	43 (48.9%)	61 (49.2%)	104 (49.1%)	178 (34.4%)
Time since initial schizophrenia diagnosis (years) <sup>a</sup>	1.8 (1.70)	12.6** (7.13)	8.1 (7.70)	2.0 (1.54)
Age at first diagnosis (years) <sup>a</sup>	31.0 (12.02)	26.8*** (8.69)	28.5 (10.38)	26.7 (7.95)
Number of psychiatric hospitalizations				NA
0–1	53 (60.2%)	38 (30.7%)	91**** (42.9%)	
2	12 (13.6%)	20 (16.1%)	32 (15.1%)	
3	6 (6.8%)	9 (7.3%)	15 (7.1%)	
> 3	15 (17.1%)	46 (37.1%)	61 (28.8%)	
Unknown	2 (2.3%)	11 (8.7%)	13 (6.1%)	
Baseline PSP total score <sup>a</sup>	42.6 (13.13)	43.0 (13.21)	42.8 (13.14)	58.5 (16.18)

For between-group differences,  $p$  values are greater than 0.5, except as noted.

NA not applicable, PSP Personal and Social Performance

\*  $p = 0.023$  based on analysis of variance (ANOVA) model; \*\*  $p < 0.0001$  based on ANOVA model; \*\*\*  $p = 0.0038$  based on ANOVA model; \*\*\*\*  $p < 0.001$  for difference in distribution based on chi-square test.

<sup>a</sup> The mean is given, with the standard deviation in parentheses.

<sup>b</sup> Eighty-seven patients

<sup>c</sup> Two hundred eleven patients

**Table 2** Personal and Social Performance total score: change from the baseline to week 13—study 1

Time point	Duration of schizophrenia		All patients
	≤ 5 years	> 5 years	
Baseline			
Number of Patients	88	124	212
Number of Missing patients	0	0	0
Mean score <sup>a</sup>	42.6 (13.13)	43.0 (13.21)	42.8 (13.14)
Week 13			
Number of Patients	75	109	184
Number of Missing patients	13	15	28
Mean change in score from baseline <sup>a</sup>	25.4 (16.22)	14.4 (17.11)	18.8 (17.56)
<i>p</i> -value <sup>b</sup>	< 0.0001	< 0.0001	< 0.0001
Summary of ANCOVA model			NA
LS mean <sup>c</sup>	25.0 (1.67)	14.6 (1.39)	
95% CI	21.72–28.33	11.85–17.33	
<i>p</i> -value <sup>d</sup>		< 0.0001	
Difference in mean scores			
LS mean <sup>c</sup>		10.4 (2.18)	
95% CI		6.14–14.73	
<i>p</i> -value <sup>d</sup>		< 0.0001	

ANCOVA analysis of covariance, CI confidence interval, LS least squares, NA not applicable

<sup>a</sup> The standard deviation is given parentheses.

<sup>b</sup> For within-group difference based on paired *t* test

<sup>c</sup> The standard error is given in parentheses.

<sup>d</sup> ANCOVA model: change from baseline score = subgroups + baseline score.

Of the 184 patients who had an unfavorable level of functioning at the baseline (PSP score of 70 or less), 54 (29.4%) improved to a favorable level (PSP score greater than 70) after 13 weeks of treatment with PP1 M. Patients with recently diagnosed schizophrenia demonstrated a greater improvement compared with those with chronic disease (30 of 75, 40%, vs 24 of 109, 22.0%, respectively;  $p < 0.0001$ ).

Improvements were demonstrated in all PSP domains (Fig. 1); the improvement was significantly ( $p < 0.05$ ) greater among those with recently diagnosed schizophrenia compared

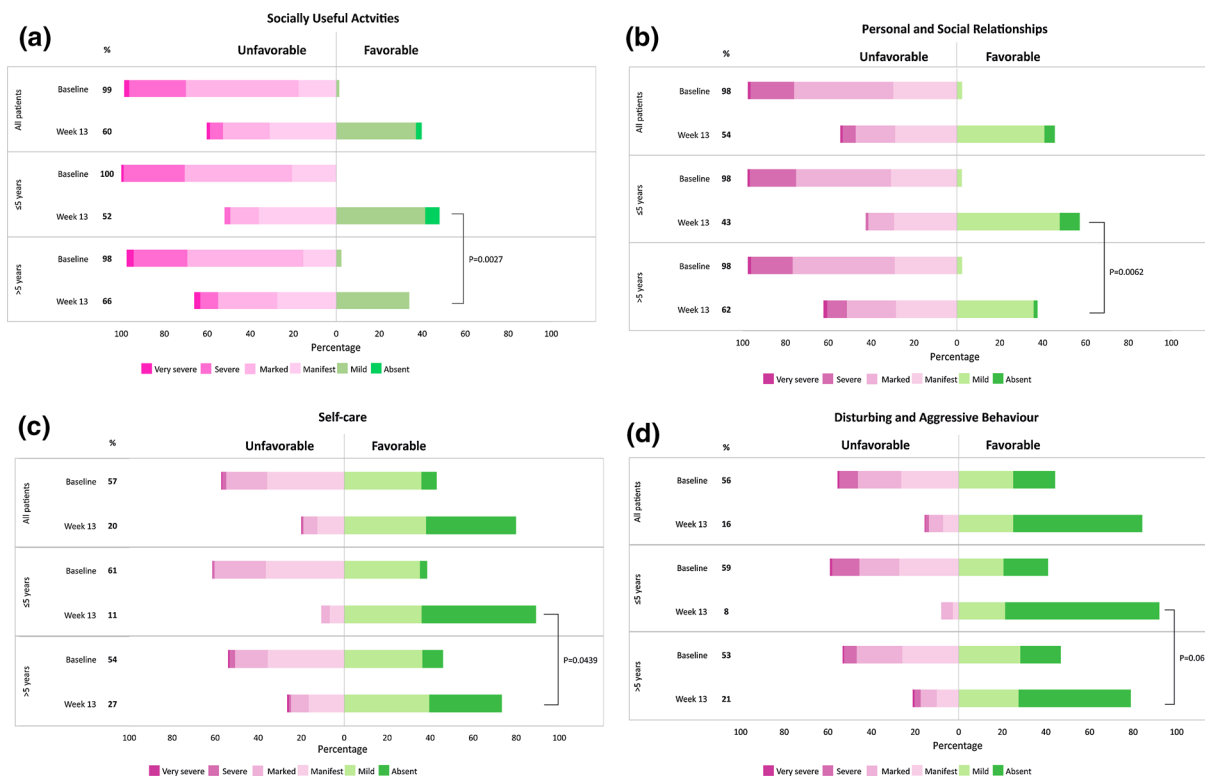
with those with chronic schizophrenia for all domains except disturbing/aggressive behavior.

## Study 2

### Patient Disposition and Clinical Characteristics

Study 2 enrolled 585 patients, 510 (87.2%) of whom were from Asian countries, and the remainder (75, 12.8%) were from Australia and New Zealand. The intent-to-treat population comprised 521 patients (64 patients were excluded because of screening failure or their





**Fig. 1** Personal and Social Performance domains at the baseline and week 13: all patients and by duration of schizophrenia—study 1. The *p* values for group difference

are based on a chi-square test or Fisher’s test when the cell counts are less than 5

having been enrolled at a site in Australia that was determined to be noncompliant with good clinical practice), 303 (58.2%) of whom completed the study. PSP data were available for 516 patients and employment data were available for 469 patients at the baseline.

Enrollees were primarily men (65.5%) and had a mean age of approximately 29 years. In this study of patients with recently diagnosed schizophrenia, most (68.9%) had received a diagnosis within the past 3 years (mean 2.0 years). Most of the study patients had functional disability at study enrolment (68.4% with varying functioning and 6.8% with a poor level of function that required intensive supervision).

**Change in Functioning with PP1M Treatment**

Significant improvement in functioning from the baseline was observed at all visits (Table 3). At month 18, the mean increase (representing

improvement) from the baseline in PSP total score was 10.5, resulting in almost half of patients (48.7%, 247/507) showing clinically meaningful improvement in functioning (i.e., 10 point or greater increase in PSP total score).

Of the 382 patients who had an unfavorable level of functioning at the baseline (PSP score of 70 or less), 153 (30.2%) improved to a favorable level (PSP score greater than 70) after 6 months of treatment with PP1 M, which was sustained after 18 months of treatment (176, 34.78%) (Table 4). This shift to a more favorable level of functioning was observed irrespective of the baseline severity of illness (i.e., baseline PANSS score; data not shown).

Functional improvement during treatment with PP1M was also reflected in significantly increased employment levels at all postbaseline visits ( $p \leq 0.0036$ ). The proportion of patients fully/partially employed was 50% greater at

**Table 3** Personal and Social Performance total score: change from the baseline during the 18-month study—study 2

Study visit	Value
Baseline	
Number of patients	516
Mean score <sup>a</sup>	58.5 (16.18)
Week 5	
Number of patients	504
Mean change in score from baseline <sup>a</sup>	5.8 (13.87)
95% CI	4.57–7.00
<i>p</i> -value <sup>b</sup>	<0.0001
Month 6	
Number of patients	507
Mean change in score from baseline <sup>a</sup>	8.7 (17.95)
95% CI	7.11–10.24
<i>p</i> -value <sup>b</sup>	< 0.0001
Month 12	
Number of patients	507
Mean change in score from baseline <sup>a</sup>	9.2 (19.05)
95% CI	7.52–10.85
<i>p</i> -value <sup>b</sup>	< 0.0001
Month 18	
Number of patients	507
Mean change in score from baseline <sup>a</sup>	10.5 (19.55)
95% CI	8.82–12.23
<i>p</i> -value <sup>b</sup>	< 0.0001

CI confidence interval

<sup>a</sup> The standard deviation is given in parentheses.

<sup>b</sup> For within-group difference based on paired *t* test

month 18 (47.9%, 134/280) as compared with the baseline (31.8%, 89/280). Sixty-six patients (of 280, 23.6%) with unemployment/out of employment status at the baseline had shifted to full employment/partial employment status at month 18, and of these patients, 52 (of 280, 18.6%; Table 5) with unemployment/out of

**Table 4** Shift in Personal and Social Performance (PSP)-measured function from the baseline—study 2

Functional status at visit	Functional status at the baseline	
	Mild	Varying/poor
Week 5		
Mild	107 (21.2%)	82 (16.3%)
Varying/poor	17 (3.4%)	298 (59.1%)
<i>p</i> -value <sup>a</sup>		< 0.0001
Month 6		
Mild	103 (20.3%)	153 (30.2%)
Varying/poor	22 (4.3%)	229 (45.2%)
<i>p</i> -value <sup>a</sup>		< 0.0001
Month 12		
Mild	98 (19.3%)	163 (32.2%)
Varying/poor	27 (5.3%)	219 (43.3%)
<i>p</i> -value <sup>a</sup>		< 0.0001
Month 18		
Mild	99 (19.5%)	176 (34.7%)
Varying/poor	26 (5.1%)	206 (40.6%)
<i>p</i> -value <sup>a</sup>		< 0.0001

The data are given as the number of participants. The baseline was defined as day 1. Missing values were imputed by the last nonmissing postbaseline value (last observation carried forward method). No imputation was done for missing baseline values. Percentages are based on the number of intent-to-treat patients assessed at each visit. Mild corresponds to a PSP total score of 71–100, varying corresponds to a PSP total score of 31–70, and poor corresponds to a PSP total score of 30 or less.

<sup>a</sup> From McNemar's (chi-square) test of symmetry, comparing the shift from the baseline to each postbaseline visit by PSP total score category

employment status at the baseline had shifted to full employment.

## DISCUSSION

Despite favorable effects on psychopathological symptoms, many patients with schizophrenia



**Table 5** Shift in employment status from the baseline—study 2

Employment status at visit	Employment status at the baseline			
	Full employment	Partial employment	Unemployment	Out of employment
Month 3 ( <i>N</i> = 390)				
Full employment	53 (13.6%)	17 (4.4%)	31 (8.0%)	3 (0.8%)
Partial employment	4 (1.0%)	21 (5.4%)	18 (4.6%)	2 (0.5%)
Unemployment	14 (3.6%)	7 (1.8%)	159 (40.8%)	7 (1.8%)
Out of employment	3 (0.8%)	2 (0.5%)	6 (1.5%)	43 (11.0%)
<i>p</i> -value <sup>a</sup>				0.0036
Month 6 ( <i>N</i> = 349)				
Full employment	44 (12.6%)	17 (4.9%)	44 (12.6%)	5 (1.4%)
Partial employment	2 (0.6%)	15 (4.3%)	16 (4.6%)	2 (0.6%)
Unemployment	12 (3.4%)	9 (2.6%)	127 (36.4%)	4 (1.2%)
Out of employment	5 (1.4%)	2 (0.6%)	6 (1.7%)	39 (11.2%)
<i>p</i> -value <sup>a</sup>				< 0.001
Month 9 ( <i>N</i> = 321)				
Full employment	44 (13.7%)	19 (5.9%)	39 (12.2%)	7 (2.2%)
Partial employment	3 (0.9%)	11 (3.4%)	11 (3.4%)	1 (0.3%)
Unemployment	7 (2.2%)	7 (2.2%)	120 (37.4%)	6 (1.9%)
Out of employment	5 (1.6%)	2 (0.6%)	5 (1.6%)	34 (10.6%)
<i>p</i> -value <sup>a</sup>				< 0.001
Month 12 ( <i>N</i> = 303)				
Full employment	45 (14.9%)	13 (4.3%)	42 (13.9%)	4 (1.3%)
Partial employment	4 (1.3%)	13 (4.3%)	11 (3.6%)	0 (0%)
Unemployment	6 (2.0%)	7 (2.3%)	101 (33.3%)	9 (3.0%)
Out of employment	4 (1.3%)	2 (0.7%)	8 (2.6%)	34 (11.2%)
<i>p</i> -value <sup>a</sup>				< 0.001
Month 15 ( <i>N</i> = 289)				
Full employment	39 (13.5%)	13 (4.5%)	41 (14.2%)	8 (2.8%)
Partial employment	4 (1.4%)	7 (2.4%)	14 (4.8%)	0 (0%)
Unemployment	11 (3.8%)	10 (3.5%)	97 (33.6%)	13 (4.5%)
Out of employment	4 (1.4%)	3 (1.0%)	4 (1.4%)	21 (7.3%)
<i>p</i> -value <sup>a</sup>				< 0.001

**Table 5** continued

Employment status at visit	Employment status at the baseline			
	Full employment	Partial employment	Unemployment	Out of employment
Month 18 ( $N = 280$ )				
Full employment	43 (15.4%)	13 (4.6%)	47 (16.8%)	5 (1.8%)
Partial employment	3 (1.1%)	9 (3.2%)	13 (4.6%)	1 (0.4%)
Unemployment	8 (2.9%)	7 (2.5%)	86 (30.7%)	14 (5.0%)
Out of employment	3 (1.1%)	3 (1.1%)	5 (1.8%)	20 (7.1%)
$p$ -value <sup>a</sup>				< 0.001

The data are given as the number of participants. The baseline was defined as the 12 months before day 1.

<sup>a</sup> From the Bowker (chi-square) test of symmetry, comparing the shift from the baseline to each postbaseline visit in employment status

treated with antipsychotic agents remain functionally impaired [5]. As deficits in psychosocial domains are a core feature of schizophrenia, efficient long-term treatment of patients with schizophrenia must effect psychosocial reintegration as well as reduce psychotic symptoms [12].

The results reported herein, based on a large cohort (total  $N = 729$ ) of patients with schizophrenia in the Asia–Pacific region, show that most patients achieved significant and clinically meaningful improvement in function in the initial 3 months of PP1M treatment. All domains of personal and social functioning were improved. These early results were sustained for 18 months among patients with recently diagnosed disease. Improvement in employment status confirmed these functional gains. Taken together, these results underscore the importance of early initiation of effective treatment for functional improvement in schizophrenia. These findings confirm and extend the primary analyses [36, 40], and are consistent with other LAI antipsychotic studies that have reported similar effects on functioning in patients with schizophrenia. Further, examination of the domain scores reported here allows a more detailed understanding of functioning over time.

The open-label design and lack of a comparator group are limitations of these studies and may have contributed to confounding as

well as observational bias of the investigators and from high expectations of patients. With this in mind, we did not evaluate if a relationship exists between improvement in functioning (PSP score) and improvement in symptom scores, although others have reported improvements in social functioning to be independent of concurrent reduction of the patients' symptoms [48, 49]. Furthermore, the subgroup analyses by duration of illness were conducted on a post hoc basis, and should therefore be considered exploratory.

Our results of early and sustained functional improvement with PP1M treatment of Asia–Pacific patients with schizophrenia are consistent with the results from other studies of primarily Western patients with schizophrenia [17–19, 22, 24–26, 28–33]. For example, in a 13-week, double-blind, global study of patients (94.5% non-Asian patients, 5.5% Asian patients) with acute schizophrenia, Pandina et al. [30] noted a mean increase in PSP total score from the baseline to the study end point of 8.5 points among 453 patients treated with PP1M. Hargarter et al. [25] reported functional improvement of a similar magnitude (based on an increase in mean PSP total score) in an open-label 6-month study of 568 patients with nonacute schizophrenia treated with PP1M.

Treatment of acutely ill patients with PP1M was associated with improvement in all four domains of functioning. There was a substantial

shift from severe/moderate toward mild/absent to absent impairment in socially useful activities, including work and study, personal/social relationships, self-care, and disturbing and aggressive behavior. These shifts are noteworthy because improvements in these domains may potentially be indicators of improved productivity, integration into society, and recovery, and they are especially important to patients and their families.

Notwithstanding these benefits, hurdles to early introduction of LAIs in the treatment of schizophrenia still exist [50]. Some patients express misgivings with injectable treatment based on fear of injection site pain, higher treatment cost (although studies prove otherwise [51, 52]), and perceived stigma [53], the latter particularly relevant for Asian patients. Slow adoption among physicians may stem from practical issues such as dose selection, inexperience with switching from an oral to an injectable formulation, and lack of institutional structure and trained staff to provide treatment [54–57]. Nevertheless, the results of this study and those of others [58] underscore the benefits of initiating treatment with LAIs early in the course of the disease for patients with schizophrenia.

## CONCLUSION

In summary, PP1M treatment was associated with prompt and sustained improvement in functioning as well as increased employment levels among Asia–Pacific patients with schizophrenia. Improvement in functionality as observed with PP1M treatment may be an important clinical consideration when an antipsychotic agent is being selected for Asia–Pacific patients with schizophrenia.

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