

Impact of time of initiation of once-monthly paliperidone palmitate in hospitalized Asian patients with acute exacerbation of schizophrenia: a post hoc analysis from the PREVAIL study

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Purpose: To evaluate the differences in efficacy and safety outcomes in acute exacerbating schizophrenia patients between 2 subgroups (≤ 1 week and > 1 week), differing in time interval from hospitalization to time of initiation of once-monthly paliperidone palmitate.

Patients and methods: PREVAIL was a multicenter, single-arm, open-label, prospective Phase IV study in hospitalized Asian patients (either sex, aged 18–65 years) diagnosed with schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition). Change from baseline to week 13 in primary (Positive and Negative Syndrome Scale [PANSS] total score), secondary endpoints (PANSS responder rate, PANSS subscale, PANSS Marder factor, Clinical Global Impression-Severity, and Personal and Social Performance scale scores, readiness for hospital discharge questionnaire) and safety were assessed in this post hoc analysis.

Results: Significant mean reduction from baseline to week 13 in the PANSS total score, 30% PANSS responder rates ($P \leq 0.01$), PANSS subscales (positive and general psychopathology; all $P \leq 0.01$), PANSS Marder factor (positive symptoms, uncontrolled hostility, and excitement and anxiety/depression; all $P \leq 0.01$), Personal and Social Performance scale scores ($P \leq 0.05$) and Clinical Global Impression-Severity categorical summary ($P \leq 0.05$) were significantly greater in the ≤ 1 week subgroup versus > 1 week subgroup ($P \leq 0.05$). The readiness for hospital discharge questionnaire improved over time for the overall study population, but remained similar between subgroups at all-time points. Treatment-emergent adverse events were similar between the subgroups.

Conclusion: Early initiation of once-monthly paliperidone palmitate in hospitalized patients with acute exacerbation of schizophrenia led to greater improvements in psychotic symptoms with comparable safety than treatment initiation following 1 week of hospitalization.

Keywords: early treatment initiation, hospital setting, long acting injectable, Asian, hospital discharge, efficacy, safety, positive and negative syndrome scale total score

Introduction

Schizophrenia is a chronic, disabling illness with the potential for acute worsening of psychotic symptoms, thus requiring long-term treatment with antipsychotics for continuous disease control.¹ The clinical management of schizophrenia remains a challenge due to non-adherence to antipsychotic treatment and patient-related issues.² As a consequence, patients often experience multiple relapses³ and manifest an acute worsening of psychotic and behavioral symptoms, requiring hospitalization during the course of illness.⁴ Treatment non-adherence within the first few days of initiation of antipsychotic medication can hinder the onset of efficacy.⁵ Therefore, an optimal

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therapy that addresses the issue of non-adherence may potentially provide more immediate relief to reduce the severity of symptoms, offer sustained relief, and enable earlier hospital discharge.

Long-acting injectable (LAI) antipsychotics, which overcome the need of daily intake of medications, have demonstrated an increased adherence in schizophrenia patients along with relapse reduction and symptom improvement.⁶ Typically, LAIs have a slow-release profile with a delayed onset of action, and thus are generally reserved for stabilized patients with difficulties in complying with oral regimens during the maintenance treatment.⁷ Once-monthly paliperidone palmitate (PP1M, Invega® Sustenna®) has a unique pharmacokinetic profile, i.e., rapidly attaining therapeutic plasma concentrations and providing a continuous release over the treatment period thus warranting its use as a preferred treatment option for patients with acute exacerbation of schizophrenia.^{8–11} Such a pharmacokinetic profile permits the use of PP1M in acutely symptomatic patients without the need of oral supplementation, improves adherence, and reduces severity of symptoms, risk of relapse, and re-hospitalizations compared with their oral counterparts.^{5,12–14}

The recently published PREVAIL study¹⁵ (parent study for this post hoc analysis) demonstrates efficacy and tolerability of PP1M in hospitalized patients with acute exacerbating schizophrenia. However, data elucidating the effect of time of initiation of LAIs after hospitalization are lacking, which are critical in clinical practice. Tolerability to oral paliperidone or oral risperidone is a prerequisite for initiating PP1M therapy; most clinical trials for PP1M conducted such “tolerability testing” by exposing patients to these drugs for about 4–6 days before PP1M therapy.¹⁶ Hence this post hoc analysis from the PREVAIL study aimed to compare the effects of initiating PP1M closer to the prescribing information supported by clinical trials (ie, ≤ 1 week) versus delaying such treatment (> 1 week) to perform tolerability test.

Methods

The PREVAIL study was a multicenter, single-arm, open-label, prospective Phase IV study. Asian patients (either sex, aged 18–65 years) meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), with a Positive and Negative Syndrome Scale (PANSS) total score of ≥ 60 , or Clinical Global Impression-Severity (CGI-S) score of ≥ 4 (moderately ill), and hospitalized with an acute exacerbation of schizophrenia within 4 weeks of screening, were enrolled in this study.

Patients with a primary active DSM-IV Axis I diagnosis other than schizophrenia, DSM-IV diagnosis of substance

dependence (except for nicotine and caffeine) within 6 months of screening, or receiving clozapine or LAI antipsychotics, including PP1M within 1 month of the screening, and are at a significant risk of suicide were excluded.¹⁵

The study consisted of a screening period (~7 days), an open-label treatment period (13 weeks), and a study completion visit (week 13, 1 month after the last dose of the PP1M injection).

On day 1, all eligible patients (Asian, either sex, aged 18–65 years) were switched to PP1M from their existing oral antipsychotics. Patients without documented tolerability to oral risperidone, extended-release (ER) paliperidone, risperidone-LAI, or PP1M were administered paliperidone ER (3 mg/day) or oral risperidone (1 mg/day) for at least 2 days during the screening period.

Patients received injections of PP1M at a starting dose of 150 mg equivalent (eq) at day 1 and 100 mg eq on day 8 (both deltoid) followed by once-monthly intramuscular maintenance doses of 75, 100, or 150 mg eq of paliperidone palmitate (deltoid or gluteal muscle) on day 36 and 64.

The study protocol was reviewed and approved by the Institutional Review Board, Medical Ethics Committee, or Medical Research and Ethics Committee of the local study sites in the participating countries (Table S1). This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and in accordance with the International Conference on Harmonization’s Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the respective protocols. All patients provided written informed consent prior to study participation.

Study assessments

The differences in efficacy and safety outcomes of patients with acute exacerbation of schizophrenia between the 2 patient subgroups (≤ 1 week and > 1 week) differing in time interval from date of hospitalization to date of first injection of PP1M were evaluated. The primary efficacy endpoint was the change from baseline to week 13 in PANSS total score. The secondary efficacy endpoints were the changes from baseline in PANSS subscale scores, PANSS Marder factor scores, PANSS responder rate, CGI-S scale, Personal and Social Performance (PSP) scale scores, and readiness for hospital discharge questionnaire (RDQ). The PANSS total score, Marder factor scores, subscales score, and responder rate were analyzed at screening, baseline, day 4, and weeks 1, 5, and 13. The CGI-S and RDQ assessments were performed at screening, baseline, and weeks 1, 5, 9, and 13. The PSP was administered at baseline and week 13.

Safety assessments included incidence or type of treatment-emergent adverse events (TEAEs), extrapyramidal symptoms (EPS)-related TEAEs, and blood prolactin-related potential TEAEs.

Statistical analysis

Efficacy and safety analyses were performed on the intent-to-treat (ITT) analysis set, which included patients who received at least 1 dose of study medication during the study. Descriptive statistics method was used to analyze all data. The changes from baseline to last observation carried forward (LOCF) end point in PANSS total score, Marder factor scores, subscale scores, CGI-S, and PSP total scores were summarized for the ITT analysis set. The changes in

these scores from baseline within each group were analyzed using a paired *t*-test. The difference in change from baseline scores between the 2 subgroups (≤ 1 week and > 1 week) were analyzed based on the LOCF data using an analysis of covariance model, with subgroup as factor and the baseline scores as the covariate. The 30% PANSS response rate (percentage of patients with at least 30% reduction in the PANSS total score from baseline to the endpoint) was calculated and compared between the groups using the Chi-square test.

The RDQ data were summarized over time by the number and percentage of patients who were ready for discharge from the hospital. The difference between the 2 subgroups in the rate of discharge was analyzed using the Chi-square or the Fisher's exact test. The number of patients with at

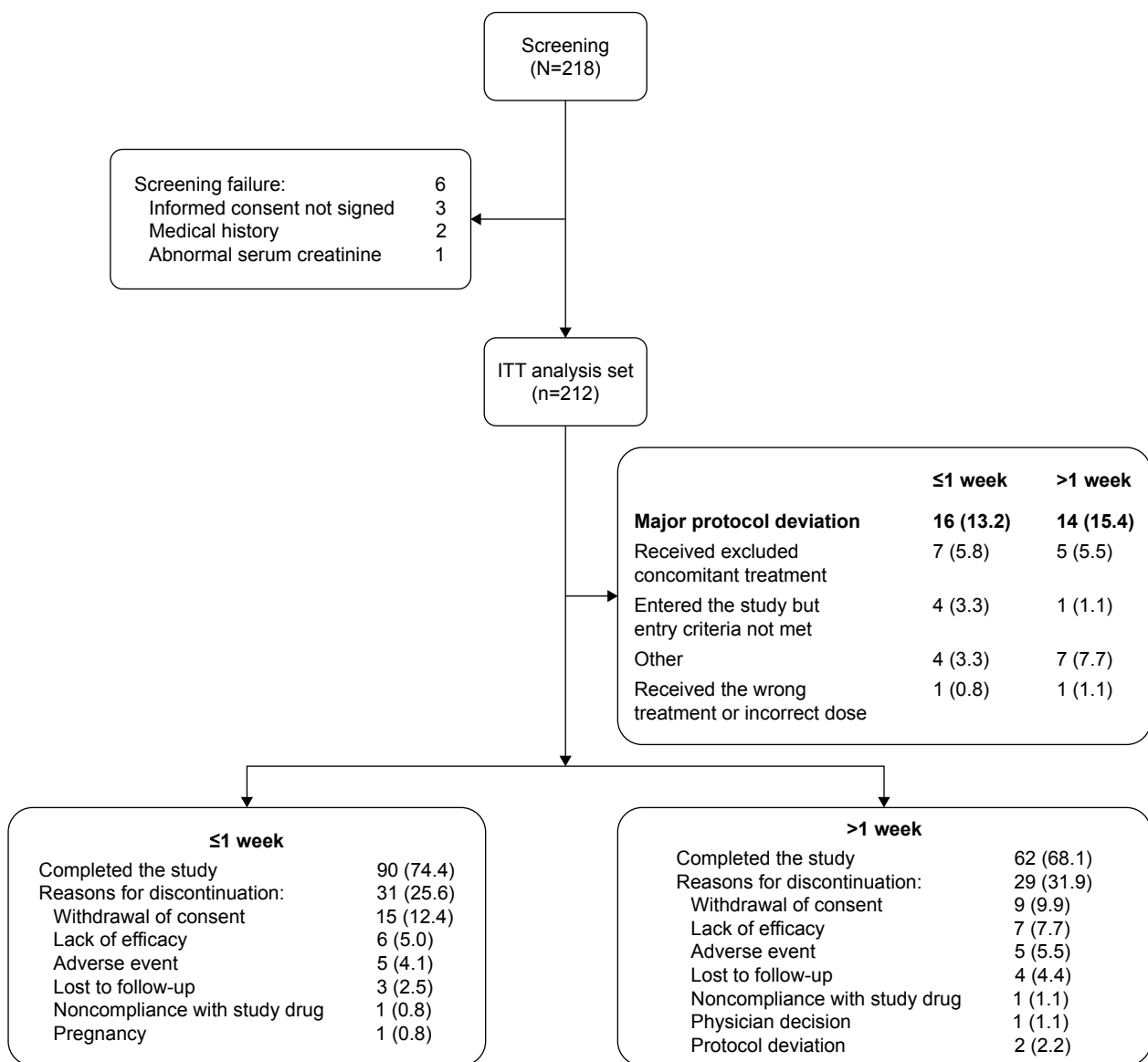


Figure 1 Patient disposition (≤ 1 week versus > 1 week).

Notes: Per protocol group, included all patients without a major protocol deviation; values are n (%).

Abbreviation: ITT, intent-to-treat.

least 1 TEAE was summarized regardless of the severity and relationship to the study medication.

Results

Patient disposition and demographics

All 212 patients from the PREVAIL study were included in this post hoc analysis (≤ 1 week, $n=121$; > 1 week, $n=91$), of which 152 (71.7%, ≤ 1 week, $n=90$; > 1 week, $n=62$) patients completed the 13-week treatment period. Discontinuations were mainly due to withdrawal of consent in both subgroups (Figure 1). The study population was 100% Asian and most baseline characteristics and demographics between the 2 subgroups were well-balanced except for the number of women, which was greater in the > 1 week subgroup (60.4%) versus the ≤ 1 week subgroup (40.5%; Table 1). Most of the patients initiated treatment within 1 week of hospitalization (Table 2).

Efficacy outcomes

Primary efficacy endpoint

The difference in mean change from baseline to week 13 in the PANSS total score significantly favored the ≤ 1 week subgroup versus the > 1 week subgroup (mean [SD]: -6.9 [2.98]; 95% CI: $(-12.81$ to $-1.07)$; $P \leq 0.05$; Figure 2). The mean change from baseline within each subgroup in PANSS total score improved significantly ($P \leq 0.0001$) at each time point of day 4, and weeks 1, 5, and 13 (Table 3).

Secondary efficacy endpoints

The 30% PANSS responder rate increased over time (Figure 3). At week 13, the 30% PANSS responder rate was significantly higher ($P \leq 0.01$) in the ≤ 1 week subgroup (n [%]: 85 [70.83%]; 95% CI: 61.84% to 78.77%) versus the > 1 week subgroup (n [%]: 49 [54.44%]; 95% CI: 43.60% to 64.98%).

The mean changes from baseline within each subgroup for PANSS Marder factor scores, CGI-S, and PSP total scores improved significantly at each time point of day 4, and weeks 1, 5, and 13 ($P \leq 0.0001$, Table 3). The differences in mean changes from baseline to week 13 between the 2 subgroups in PANSS subscales (positive and general psychopathology) and PANSS Marder factor (positive symptoms, uncontrolled hostility and excitement, and anxiety/depression) were significant (Table 4).

The difference in mean changes (SD) from baseline to week 13 in CGI-S scale score were similar between the 2 subgroups (≤ 1 week: -1.5 [0.21]; > 1 week: -1.3 [1.48], Table 3). At week 13, the difference in mean CGI-S categorical summary was significant ($P \leq 0.05$) between the 2 subgroups,

Table 1 Demographics and baseline characteristics (ITT population)

Characteristics	≤ 1 week ($n=121$)	> 1 week ($n=91$)
Age, years, mean (SD)	36.2 (12.15)	38.4 (11.32)
Age range, years, n (%)		
18–25	28 (23.1)	15 (16.5)
26–50	73 (60.3)	60 (65.9)
> 50	20 (16.5)	16 (17.6)
Sex, n (%)		
Men	72 (59.5)	36 (39.6)
Women	49 (40.5)	55 (60.4)
BMI, kg/m ² , mean (SD)	23.3 (3.97)	24.0 (4.58)
Weight category, n (%)		
Normal (< 25)	87 (72.5)	60 (65.9)
Overweight (25 to < 30)	26 (21.7)	21 (23.1)
Obese (≥ 30)	7 (5.8)	10 (11.0)
Age in years at first schizophrenia diagnosis, mean (SD)	29.4 (12.19)	30.2 (9.81)
Previous psychiatric hospitalizations, n (%)		
0	19 (15.7)	16 (17.6)
≥ 1	96 (79.3)	68 (74.7)
Unknown	6 (5.0)	7 (7.7)
Current hospitalization at enrolment, mean (SD)	36.4 (28.09)	40.2 (26.60)
Baseline PANSS total score, mean (SD)	89.1 (14.99)	91.1 (20.21)
Baseline CGI-S scale score, mean (SD)	4.9 (0.78)	4.9 (0.82)
Mild illness, n (%)	3 (2.5)	3 (3.3)
Moderate illness, n (%)	34 (28.1)	25 (27.5)
Marked, severe/extremely severe illness, n (%)	84 (69.4)	63 (69.2)
Baseline PSP score, mean (SD)	43.8 (12.27)	41.5 (14.19)
PSP-score categorical summary, n (%)		
Poor	26 (21.5)	24 (26.4)
Varying	95 (78.5)	65 (71.4)
Mild	0 (0.0)	2 (2.2)

Abbreviations: BMI, body mass index; CGI-S, clinical global impression-severity; ITT, intent-to-treat; PANSS, positive and negative syndrome scale; PSP, personal and social performance; SD, standard deviation.

with patients in the > 1 week subgroup having almost 2 times more severe (≤ 1 week, 6 [5.04%]; > 1 week, 9 [10.23%]) and extremely severe patients versus the ≤ 1 week subgroup (≤ 1 week, 0 [0%]; > 1 week, 2 [2.27%]; Table 5).

The difference in mean changes from baseline to week 13 in PSP scale score between the 2 subgroups was significant

Table 2 Distribution of time to treatment initiation

Time interval	n	%	Cumulated number	Cumulated number (%)
Day 1	13	6.13	13	6.13
1 day to ≤ 1 week	108	50.94	121	57.08
1 week to ≤ 2 weeks	47	22.17	168	79.25
2 weeks to ≤ 4 weeks	36	16.98	204	96.23
> 4 weeks	8	3.77	212	100.00

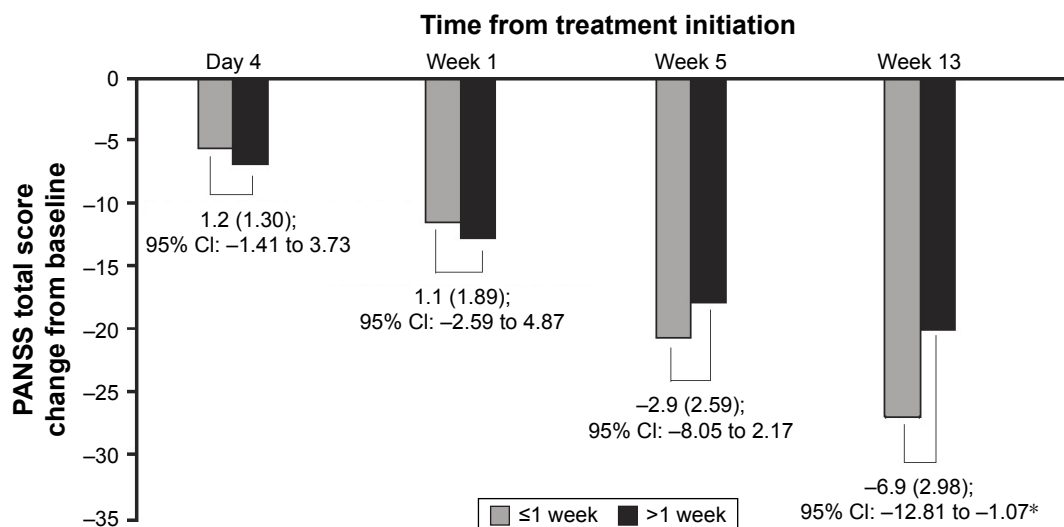


Figure 2 Difference in mean change in PANSS total score at various time points.

Notes: All values are least square means (standard error); * $P \leq 0.05$; difference between subgroups, ≤ 1 week minus > 1 week.

Abbreviations: CI, confidence interval; PANSS, positive and negative syndrome scale.

($P \leq 0.05$; Table 4). At week 13, the overall PSP score categorical summaries were similar between the 2 subgroups ($P = 0.124$), with almost 3 times more patients in the poor category in the > 1 week (8 [10.00%]) subgroup versus the ≤ 1 week subgroup (3 [2.88%]; Table 5).

The number of patients ready for hospital discharge (including RDQ assessments and actual hospital discharge) improved over time but remained similar between subgroups at all-time points. At week 13, the number of patients ready for hospital discharge was similar in both subgroups (≤ 1 week, 78 [75.0%]; > 1 week groups, 55 [69.6%], $P = 0.419$; Figure 4).

Safety

The percentages of patients experiencing at least 1 TEAE or TEAEs leading to treatment discontinuation were similar in both subgroups (Table 6). The percentage of patients with serious TEAEs (≤ 1 week, 3.3%; > 1 week, 11.0%) and discontinuations due to TEAE (≤ 1 week, 5 [4.13%]; > 1 week, 5 [5.49%]) were comparatively less in the ≤ 1 week subgroup. The top 5 most commonly reported TEAEs in the ≤ 1 week subgroup were nasopharyngitis (12.4%), constipation (10.7%), weight increased (9.1%), and insomnia (9.1%), while in the > 1 week subgroup, they were schizophrenia exacerbation (8.8%), akathisia (6.6%), tremor (6.6%), insomnia (6.6%), and constipation (6.6%). Extrapyramidal TEAEs were similar in both subgroups. The incidence of blood prolactin abnormal/increased was relatively higher in the ≤ 1 week subgroup (11.6%) versus > 1 week subgroup (5.5%),

but the incidence of patients with prolactin-related symptoms was low and similar in both subgroups groups.

Discussion

To the best of our knowledge, this is one of the few studies evaluating the effect of early initiation of LAIs in patients with acute exacerbation of schizophrenia. In this post hoc analysis, patient subgroups were based on the time interval from the date of hospitalization to the date of first injection of PP1M treatment. Significant improvements in PANSS total score with early initiation of PP1M (≤ 1 week) versus delayed initiation (> 1 week) of hospitalization were observed. Similarly, significant improvements favoring the ≤ 1 week subgroup in PANSS total score, PANSS responder rates, PANSS subscales (positive and general psychopathology), PANSS Marder factor (positive symptoms, uncontrolled hostility, and excitement and anxiety/depression), and PSP scale scores were observed at week 13. Furthermore, numerical improvements favoring the ≤ 1 week subgroup in PANSS subscales score (negative), PANSS Marder factor scores (negative symptoms and disorganized thoughts) at week 13 were also observed. While the full impact of treatment was seen at week 13, patients started responding as early as day 4 to 1 week. The longer patients were on medications, the greater the response. The best way to ensure consistent medication delivery in the long term is with an LAI.

Hospital discharge, as determined using the RDQ, increased over the study treatment period in both subgroups.

Table 3 Change from baseline to each time point within subgroups

Parameters	Change from baseline to:																		
	Baseline			Day 4			Week 1			Week 5			Week 9			Week 13			
	≤ 1 week (n=121)	> 1 week (n=91)	ND	≤ 1 week (n=121)	> 1 week (n=91)	ND	≤ 1 week (n=121)	> 1 week (n=91)	ND	≤ 1 week (n=121)	> 1 week (n=91)	ND	≤ 1 week (n=121)	> 1 week (n=91)	ND	≤ 1 week (n=121)	> 1 week (n=91)	ND	
PANSS total score	89.1 (14.99)	91.1 (20.21)	ND	-5.6 (8.65)	-6.8 (10.04)	ND	-11.3 (11.53)	-12.9 (16.60)	ND	-20.3 (16.69)	-18.3 (23.87)	ND	-26.4 (19.38)	-20.6 (27.31)	ND	-26.4 (19.38)	-20.6 (27.31)	ND	
CGI-S score	4.9 (0.78)	4.9 (0.82)	ND	ND	ND	ND	-0.6 (0.61)	-0.7 (0.87)	ND	-1.2 (1.01)	-0.9 (1.13)	ND	-1.5 (1.21)	-1.3 (1.48)	ND	-1.5 (1.21)	-1.3 (1.48)	ND	
PSP score	43.8 (12.27)	41.5 (14.19)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	19.8 (16.50)	17.6 (18.89)	ND	19.8 (16.50)	17.6 (18.89)	ND	
PANSS subscales score																			
Positive subscale score	21.6 (6.28)	23.5 (6.73)	ND	-1.8 (2.90)	-2.5 (4.47)	ND	-3.6 (3.82)	-4.7 (6.60)	ND	-6.4 (6.17)	-6.3 (8.17)	ND	-8.2 (6.98)	-7.0 (8.99)	ND	-8.2 (6.98)	-7.0 (8.99)	ND	
Negative subscale score	23.4 (6.70)	22.7 (7.83)	ND	-1.2 (2.59)	-1.3 (2.29)	ND	-2.3 (3.37)	-2.4 (4.30)	ND	-4.4 (5.14)	-3.8 (6.47)	ND	-5.8 (6.03)	-4.5 (7.72)	ND	-5.8 (6.03)	-4.5 (7.72)	ND	
General psychopathology score	44.1 (8.52)	44.9 (11.46)	ND	-2.6 (4.94)	-3.0 (5.73)	ND	-5.5 (6.55)	-5.8 (8.98)	ND	-9.5 (8.70)	-8.2 (12.44)	ND	-12.4 (10.30)	-9.1 (14.18)	ND	-12.4 (10.30)	-9.1 (14.18)	ND	
PANSS Marder factor scores																			
Positive symptoms	26.2 (6.26)	27.5 (6.23)	ND	-1.5 (3.22)	-1.9 (3.58)	ND	-3.4 (4.08)	-3.9 (5.28)	ND	-6.2 (5.96)	-6.2 (7.52)	ND	-8.4 (7.08)	-6.6 (8.75)	ND	-8.4 (7.08)	-6.6 (8.75)	ND	
Negative symptoms	23.0 (6.95)	22.2 (7.93)	ND	-1.1 (2.56)	-1.5 (2.56)	ND	-2.2 (3.63)	-2.5 (4.43)	ND	-4.2 (5.35)	-3.8 (6.69)	ND	-5.5 (6.37)	-4.5 (7.92)	ND	-5.5 (6.37)	-4.5 (7.92)	ND	
Disorganized thoughts	20.1 (5.05)	19.7 (5.93)	ND	-1.2 (2.28)	-1.3 (2.54)	ND	-2.3 (3.06)	-2.4 (3.96)	ND	-4.3 (4.11)	-3.4 (5.46)	ND	-5.6 (5.22)	-4.1 (6.46)	ND	-5.6 (5.22)	-4.1 (6.46)	ND	
Uncontrolled hostility and excitement	11.2 (4.00)	11.3 (4.28)	ND	-1.1 (2.88)	-1.4 (2.63)	ND	-2.3 (3.21)	-2.4 (3.92)	ND	-3.8 (4.64)	-3.0 (5.44)	ND	-4.5 (4.59)	-3.1 (5.60)	ND	-4.5 (4.59)	-3.1 (5.60)	ND	
Anxiety/depression	8.6 (3.68)	10.5 (4.33)	ND	-0.6 (1.43)	-0.8 (2.22) ^{***}	ND	-1.2 (2.42)	-1.7 (3.26)	ND	-1.8 (2.66)	-2.0 (3.78)	ND	-2.4 (3.12)	-2.3 (3.91)	ND	-2.4 (3.12)	-2.3 (3.91)	ND	

Notes: All values are mean (standard deviation), $P \leq 0.0001$ for change from baseline using paired t-test for all parameters except those marked differently with $^{***}P \leq 0.001$.

Abbreviations: CGI-S, clinical global impression-severity; ND, not determined; PANSS, positive and negative syndrome scale; PSP, personal and social performance.

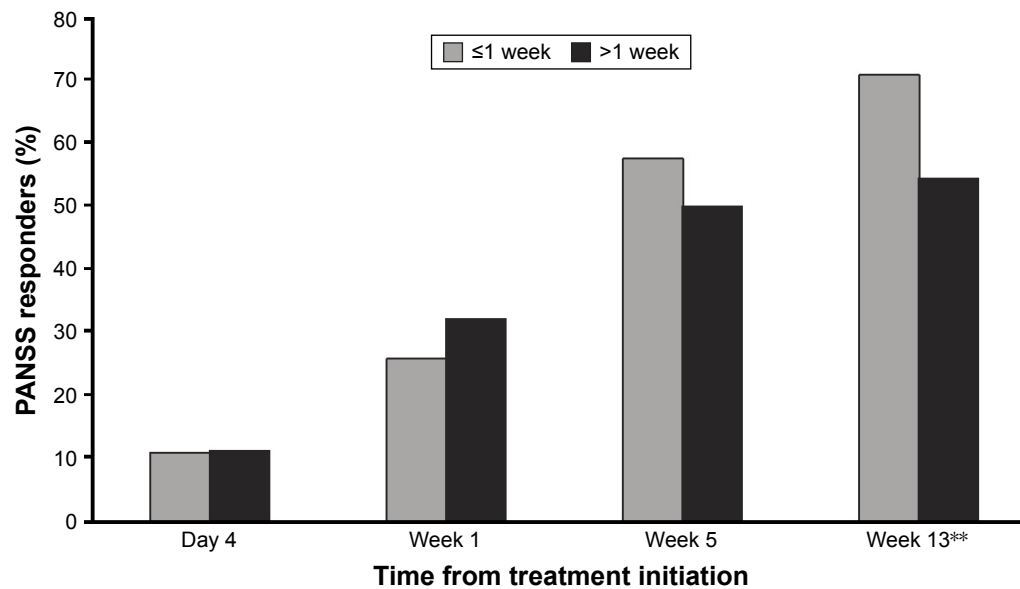


Figure 3 PANSS responder rates (>30%) at various time points.

Note: ** $P \leq 0.01$ for difference in PANSS responder rates between the subgroups.

Abbreviation: PANSS, positive and negative syndrome scale.

This increase in hospital discharge could be due to reduced symptoms and improved functioning; however, the difference between the groups was not completely evident and this could be due to the short duration of the study or small number of patients in each subgroup. The completion rates were close to 70%, suggesting acceptability of the results for endpoint interpretation, especially considering that 70% of the patients were in the “markedly severe,” “severe,” or “extremely severe” ill category.

The efficacy of LAIs for the treatment of schizophrenia is comparable or greater to that of oral antipsychotics.¹⁷ However, LAIs have been recommended as maintenance treatment, and preferred treatment for reducing the risk of relapse and to address non-adherence, with limited recommendation for use in treating early schizophrenia.¹⁸ Whereas significant improvement in psychotic symptoms without oral antipsychotic augmentation in patients with acute schizophrenia as early as on day 8 and consistent thereafter

Table 4 Changes from baseline to week 13 in the secondary endpoints

Parameter	Baseline; mean (SD)		Change from baseline to week 13; mean (SD)		Difference ^a between subgroups least square mean (SE); (95% CI)
	≤1 week (n=121)	>1 week (n=91)	≤1 week (n=121)	>1 week (n=91)	
PANSS subscales score					
Positive subscale score	21.6 (6.28)	23.5 (6.73)	-8.2 (6.98)	-7.0 (8.99)	-2.5 (0.93); (-4.35 to -0.70)**
Negative subscale score	23.4 (6.70)	22.7 (7.83)	-5.8 (6.03)	-4.5 (7.72)	-0.9 (0.76); (-2.38 to 0.62)
General psychopathology score	44.1 (8.52)	44.9 (11.46)	-12.4 (10.30)	-9.1 (14.18)	-3.8 (1.54); (-6.84 to -0.77)**
PANSS Marder factor scores					
Positive symptoms	26.2 (6.26)	27.5 (6.23)	-8.4 (7.08)	-6.6 (8.75)	-2.6 (0.98); (-4.50 to -0.65)**
Negative symptoms	23.0 (6.95)	22.2 (7.93)	-5.5 (6.37)	-4.5 (7.92)	-0.6 (0.78); (-2.13 to 0.95)
Disorganized thoughts	20.1 (5.05)	19.7 (5.93)	-5.6 (5.22)	-4.1 (6.46)	-1.2 (0.71); (-2.64 to 0.15)
Uncontrolled hostility and excitement	11.2 (4.00)	11.3 (4.28)	-4.5 (4.59)	-3.1 (5.60)	-1.6 (0.56); (-2.67 to -0.47)**
Anxiety/depression	8.6 (3.68)	10.5 (4.33)	-2.4 (3.12)	-2.3 (3.91)	-1.0 (0.39); (-1.82 to -0.26)**
CGI-S score	4.9 (0.78)	4.9 (0.82)	-1.5 (1.21)	-1.3 (1.48)	-0.2 (0.17); (-0.58 to 0.10)
PSP score	43.8 (12.27)	41.5 (14.19)	19.8 (16.50)	17.6 (18.89)	4.5 (2.28); (-0.05 to 8.96)*

Notes: * $P \leq 0.05$; ** $P \leq 0.01$ based on ANCOVA model for differences between the subgroup; ^adifference between groups ≤ 1 week minus > 1 week; based on ANCOVA model; change from baseline are least squares mean (standard deviation) based on ANCOVA model.

Abbreviations: ANCOVA, analysis of covariance; CGI-S, clinical global impression-severity; PANSS, positive and negative syndrome scale; PSP, personal and social performance; SD, standard deviation; SE, standard error.

Table 5 Categorical summary of clinical global impression-severity and personal and social performance scores

CGI-S categorical summary	Baseline		Week 13	
	≤1 week (n=121)	>1 week (n=91)	≤1 week (n=119)	>1 week (n=88)
Not ill	0 (0.00)	0 (0.00)	3 (2.52)	2 (2.27)*
Very mild	0 (0.00)	0 (0.00)	20 (16.81)	22 (25.00)*
Mild	3 (2.48)	3 (3.30)	50 (42.02)	23 (26.14)*
Moderate	34 (28.10)	25 (27.47)	28 (23.53)	15 (17.05)*
Markedly severe	56 (46.28)	42 (46.15)	12 (10.08)	15 (17.05)*
Severe	28 (23.14)	20 (21.98)	6 (5.04)	9 (10.23)*
Extremely severe	0 (0.00)	1 (1.10)	0 (0.00)	2 (2.27)*
PSP-score categorical summary	≤1 week (n=121)	>1 week (n=91)	≤1 week (n=104)	>1 week (n=80)
Poor (≤30)	26 (21.49)	24 (26.37)	3 (2.88)	8 (10.00)
Varying (>30 to ≤70)	95 (78.51)	65 (71.43)	70 (67.31)	48 (60.00)
Mild (>70)	0 (0.00)	2 (2.20)	31 (29.81)	24 (30.00)

Notes: All values are n (%); *P=0.05 based on ANCOVA model for differences between the subgroup.

Abbreviations: ANCOVA, analysis of covariance; CGI-S, clinical global impression-severity; PSP, personal and social performance.

has been observed with PP1M treatment versus oral antipsychotics and placebo.^{19,20} These results support the findings of the current study, which demonstrated early onset of efficacy on initiating PP1M, even in hospitalized patients with acute exacerbating schizophrenia.

The TEAEs were comparable between both subgroups. Serious TEAEs and TEAEs leading to treatment discontinuations were relatively lower in the ≤1 week subgroup. Treatment non-adherence, which, in majority of cases, is related with EPS, is associated with relapse.²¹ In this study, the incidence of EPS-related TEAEs were comparable between the subgroups. The incidence of blood prolactin abnormal/increased was relatively higher in the ≤1 week subgroup (11.6%) versus the >1 week subgroup (5.5%),

but the incidence of patients with prolactin-related symptoms was low and similar in both subgroups. No discontinuation due to prolactin-related TEAE was observed.

The overall improvements in terms of change from baseline within each subgroup were similar with the previously reported results for the overall population in PANSS total score, PANSS responder rates, PANSS subscales, PANSS Marder factor, CGI-S, and PSP scale scores.¹⁵

The limitations of the PREVAIL study include an open-label design, short duration of the study, a lack of comparator group to better assess the efficacy, and minimize the possible confounding variables. In addition, this post hoc analysis, which was not pre-specified at the time of design of the PREVAIL study, further limits its ability to make

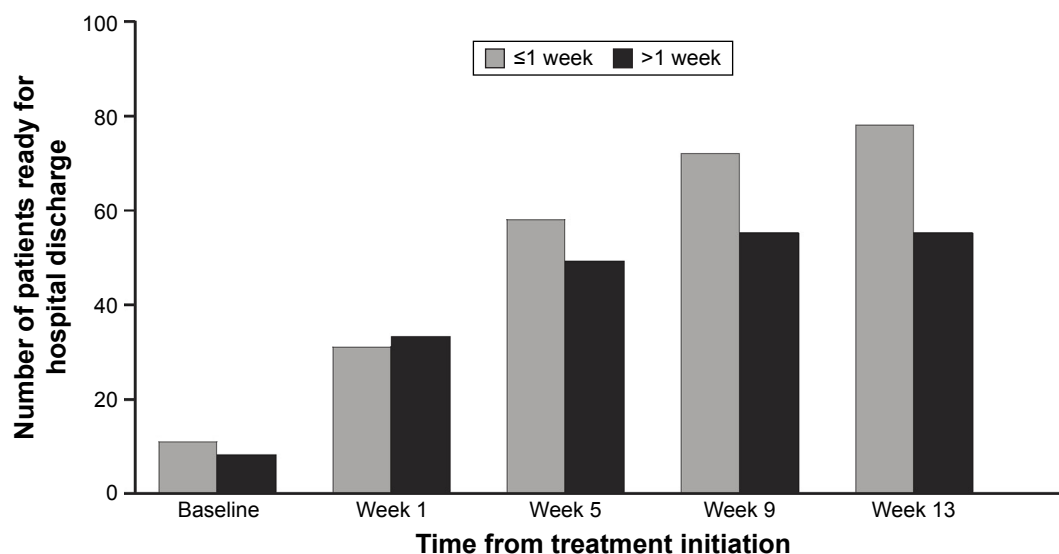


Figure 4 Summary of readiness for hospital discharge.

Table 6 Summary of treatment-emergent adverse events

Parameter	≤ 1 week (n=121)	> 1 week (n=91)
Number of patients with at least 1 TEAE	80 (66.1)	59 (64.8)
TEAEs leading to death	0	0
Serious TEAEs (≥ 1 in any subgroup)	4 (3.3)	10 (11.0)
TEAEs leading to treatment discontinuation	5 (4.13)	5 (5.49)
Most common TEAEs (≥5% in any subgroup)		
Nasopharyngitis	15 (12.4)	3 (3.3)
Constipation	13 (10.7)	6 (6.6)
Weight increased	11 (9.1)	5 (5.5)
Insomnia	11 (9.1)	6 (6.6)
Upper respiratory tract infection	6 (5.0)	4 (4.4)
Sinus bradycardia	6 (5.0)	3 (3.3)
Agitation	6 (5.0)	0
Tremor	5 (4.1)	6 (6.6)
Akathisia	4 (3.3)	6 (6.6)
Schizophrenia exacerbation	0	8 (8.8)
TEAEs of clinical interest		
Extrapyramidal symptom TEAE	22 (18.2)	15 (16.5)
Glucose-related TEAE	1 (0.8)	0
Prolactin-related TEAE	20 (16.5)	9 (9.9)
Blood prolactin abnormal/increased	14 (11.6) ^a	5 (5.5)
Hyperprolactinemia	4 (3.3)	2 (2.2)
Erectile dysfunction	1 (0.8)	0
Galactorrhoea	0	1 (1.1)
Amenorrhoea	0	1 (1.1)
Menstruation delayed	1 (0.8)	0
Prolactinoma	1 (0.8)	0

Notes: All values are n (%); ^aone case of abnormal prolactin level representing either an increase or decrease from the normal range.

Abbreviation: TEAE, treatment-emergent adverse event.

definitive conclusions. Additional long-term comparative studies are required to validate the results of this post hoc analysis to guide the optimal time for initiation of PP1M in the treatment, especially at the acute stages, of schizophrenia.

Conclusion

In this post hoc analysis from a 13-week study in hospitalized patients with acute exacerbation of schizophrenia, significant improvement from baseline in clinical symptoms and psychosocial functioning were observed irrespective of the time of treatment initiation with PP1M following hospitalization. Treatment initiation with PP1M in 1 week or less following hospitalization resulted in significantly greater improvements in clinical symptoms and psychosocial functioning with comparable safety when compared with PP1M treatment initiation following 1 week of hospitalization.

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Author contributions

All authors have provided substantial contribution for the study conception, design, acquisition of data, and analysis and interpretation of data as per the journal guidelines. All authors were involved in drafting/revising this manuscript for important intellectual content and have given final approval of the version to be published.

Disclosure

YF and WT are employees of Janssen Pharmaceutical Companies of Johnson and Johnson, Singapore. JZ is an employee of Janssen China Research and Development, Shanghai, China. IT and MM are employees of Janssen Research & Development LLC, Titusville, New Jersey, USA. The other authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Institutional Review Board/Committees

Country	Institutional Review Board/Committee (name and address)
China	IRB, Shanghai Mental Health Center (for 5 sites), No 600 Wanping South Rd., Shanghai, 200030, China IRB, Wuxi Mental Hospital No 156, Qianrong Road, Wuxi, 214151, China
Korea	IRB, Chonbuk National University Hospital 20, Geonjiro, Deokjin-gu, Jeonju-si, Jeollabuk-do 561-712, Korea IRB, Korea University Guro Hospital 148, Gurodong-ro, Guro-gu, Seoul 152-703, Korea IRB, Korea University Anam Hospital 73, Incheon-ro, Seongbuk-gu, Seoul 136-705, Korea IRB, The Catholic Univ. of St Vincent's Hospital, Building B1F, 93, Jungbu-daero, Paldal-gu, Gyeonggi-do, 442-723, Korea IRB, NHIS Ilsan Hospital, 2F, 100 Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, 410-719, Korea IRB, KyungHee University Hospital, 23 Kyunghee-daero, Dongdaemoon-du, Seoul, 130-702, Korea IRB, Asan Medical Center 88, Olympic-ro 43-gil, Songpa-gu, Seoul, 138-736, Korea IRB, Inje University Ilsan Paik Hospital 170, Juhwa-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, 411-706, Korea IEC (Clinical Trial), Ewha Womans University Hospital 1071, Anyangcheon-ro, Yangcheon-gu, Seoul 158-710, Korea IRB, Heaundae Paik Hospital 1435 Jwadong Heaudeagu, Busan, 612-030, Korea
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