

Asian Subgroup Analysis of the REMISSIO Study: A Long-Term Efficacy and Safety Study of Paliperidone Palmitate 3-month Formulation in Patients with Stable Schizophrenia in a Naturalistic Clinical Setting

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Objective: To evaluate the long-term efficacy and safety of three-monthly paliperidone palmitate (PP3M) in Asian patients with stable schizophrenia in a naturalistic setting.

Methods: Asian patients recruited between May 2016 and March 2018 from the prospective, single-arm, non-randomized, open-label, multi-national REMISSIO study were analyzed. Patients received PP3M over 12 months following ≥ 4 months of treatment with one-monthly paliperidone palmitate. The primary efficacy endpoint was the proportion of patients who achieved symptomatic remission. Other endpoints were changes in Positive and Negative Syndrome Scale (PANSS) and Personal and Social Performance (PSP) total scores, hospitalization rates, and safety.

Results: A total of 71 patients (23.3%) were Asian (South Korea: 33, Malaysia: 21, Taiwan: 17); 95.8% of patients completed the study. At LOCF, 71% of Asian patients achieved symptomatic remission compared to the overall population ($n = 172/303$, 56.8%). Improvements in mean (standard deviation) PANSS and PSP total scores from baseline to LOCF in Asian patients and overall population were clinically significant. A lower proportion of Asian patients had ≥ 1 psychiatric hospitalization after PP3M treatment ($n = 1/70$, 1.4%) than during the 12 months before ($n = 12/70$, 17.1%); compared with patients in the overall population after ($n = 8/303$, 2.6%) and before PP3M treatment ($n = 37/303$, 12.2%). The overall incidence of treatment-emergent adverse events across Asian patients was 62.9% compared to 53.1% in the overall population. Safety findings were consistent with the known safety profile of PP3M.

Conclusion: Our findings confirm existing evidence on the efficacy and tolerability of PP3M in Asian patients with stable schizophrenia over 12 months of treatment.

KEY WORDS: Paliperidone palmitate; Injections; Schizophrenia; Asia; Antipsychotic agents.

INTRODUCTION

Symptomatic remission is an important milestone in the management of schizophrenia [1]. Without adequate symptom control, patients continue to suffer from disruptions in lifestyle, productivity and an increased risk of

hospitalization [1]. While antipsychotic medications are effective for managing schizophrenia [2], prevalent non-adherence amongst patients with schizophrenia renders symptomatic remission difficult to achieve [3].

Non-adherence to medication is a common challenge with chronic illnesses [4]. However, several factors can make non-adherence especially challenging in schizophrenia [3]. Social isolation, a lack of illness awareness and positive and negative symptoms, including cognitive impairment and depression, can reduce adherence and compromise effective treatment [2,3]. In addition to the difficulty in achieving remission, studies have found that

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non-adherence in patients with schizophrenia was significantly associated with increased risk of relapse, hospitalization and suicide attempts [5]. Non-adherence also negatively affects healthcare resource utilization [6] and contributes to the disease burden of schizophrenia [7].

Long-acting injectable (LAI) antipsychotics were developed to overcome the problem of non-adherence in schizophrenia [8]. Long-acting formulations enable plasma drug concentration to be sustained over extended periods of time, thereby reducing the need for frequent dosing; and can also be used to indicate non-adherence when the patient fails to receive a follow-up injection administered by healthcare professionals [9]. Pragmatically designed studies that recruit patients under real-world clinical conditions consistently showed the superiority of LAIs over oral antipsychotics in improving remission rates [10] and reducing hospitalization rates [11,12], which is an appropriate alternative measure for relapse [11,12]. Anderson *et al.* [10] reported higher remission rates in patients who received paliperidone palmitate LAI than patients who received second-generation oral antipsychotics (45% vs. 23%; $p = 0.001$), which are often first-line pharmacological treatment of choice for schizophrenia [13]. Improvement in relapse rates or rehospitalization was demonstrated in several studies. The PROSIPAL (Prevention of Relapse with Oral Antipsychotics versus Injectable Paliperidone Palmitate) study demonstrated that relapse of schizophrenia was lower in patients who received paliperidone palmitate 1-month formulation (PP1M) than in patients who received oral antipsychotics (15% vs. 21%; $p = 0.03$) [14]. Furthermore, the risk of rehospitalization was lowest with PP1M (hazard ratio: 0.51; 95% confidence interval [CI]: 0.41–0.64) and 22% lower with LAIs compared with oral antipsychotics [15]; while treatment failure as a result of psychiatric hospitalization was more common with oral antipsychotics compared with PP1M (12% vs. 8%) [16].

Paliperidone palmitate 3-month formulation (PP3M) is an LAI administered once every three months for the treatment of schizophrenia [17]. Indicated for patients previously stabilized on PP1M [17], PP3M extends the benefits of sustained exposure and further reduced the dosing frequency. Results from two global phase III trials show that PP3M was well-tolerated, beneficial at delaying time to relapse when compared to placebo [18], and was non-inferior to PP1M in reducing the risk of relapse [6].

Research has found that the extent and pattern of schizophrenic symptoms can manifest differently across ethnicities [19]. The only study of PP3M in East Asian patients from China, Japan, South Korea, and Taiwan was a subgroup analysis of the primary randomized, double-blind, non-inferiority, fixed-dose, international study comparing PP3M and PP1M [6].

REMISSIO is a 52-week, single-arm, open-label, prospective, multicenter, international phase IIIb study on the transition to PP3M in patients with schizophrenia previously stabilized on PP1M [20]. The intent of the REMISSIO study was to mimic, as closely as possible, real-life treatment within regular clinical practice in a diverse population of patients. Therefore, as opposed to randomized controlled trials, a relatively less restrictive set of entry criteria was applied to enable the enrollment of a study population that was more naturalistic (including those with comorbidities, on various concomitant medications or with substance use issues). To our knowledge, PP3M has not been evaluated in Asian populations under such naturalistic clinical settings that allowed physicians to modify doses of PP3M and concomitant medications as needed.

In this present study, we report the findings from a subgroup analysis of Asian patients from the primary REMISSIO study. We specifically evaluated the long-term efficacy and safety of PP3M in the Asian subgroup with clinically stable schizophrenia in a naturalistic setting. We sought to investigate symptomatic remission rates amongst Asian patients treated with PP3M over the 12-month treatment period.

METHODS

Study Design

The REMISSIO study design and its primary findings have been described in detail elsewhere [20]. In brief, REMISSIO was a prospective, single-arm, non-randomized, open-label, multi-center study conducted between May 2016 and March 2018 at 57 sites across Europe, the Middle East, Africa and the Asia Pacific region (10 sites; three countries—South Korea, Malaysia, Taiwan) [20].

The REMISSIO study comprised a 1-week screening phase followed by a 12-month, open-label, flexible-dosed PP3M treatment phase. This study was registered with ClinicalTrials.gov (Identifier: NCT02713282). The

study protocol was reviewed and approved by an Independent Ethics Committee/Institutional Review Board for each site before study initiation. The study was conducted in accordance with the principles of Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice, and the applicable regulatory requirements. Written informed consent was obtained from all patients before study enrollment.

Study Population

Patients aged 18–50 years (inclusive) with a current schizophrenia diagnosis (defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition) were eligible for the current study if they had been adequately stabilized with PP1M at a dose of 50–150 mg equivalent of paliperidone (eq.) for at least 4 months with the last 2 doses of PP1M being the same, and had a Positive and Negative Syndrome Scale (PANSS) total score < 70 at screening and at baseline. Key exclusion criteria included: psychiatric diagnosis due to direct pharmacological effects of a substance or a general medical condition, diagnosis of dissociative disorder, bipolar disorder, major depressive disorder, schizoaffective disorder, autistic disorder, or intellectual disabilities, and severe substance abuse with the exception of nicotine and caffeine within 6 months prior to screening. Patients who were considered to be at imminent risk of suicide, or who received clozapine within last 3 months or other LAIs within last 4 months of screening were also excluded.

Treatment

Eligible patients were stabilized on PP1M for at least 4 months before receiving PP3M once every 3 months. A total of 4 injections of PP3M were given during the 12-month treatment phase on Day 1, Month 3, Month 6, and Month 9. The first dose of PP3M should be 3.5-fold higher than the last PP1M dose, and subsequent doses of PP3M can be adjusted in increments within the range of 175 mg eq. to 525 mg eq. based on the patient's tolerability and/or efficacy and according to the product label.

Study Endpoints

The primary efficacy endpoint was the proportion of patients who achieved symptomatic remission at study endpoint (last observation carried forward [LOCF]; i.e., Month 12 or early discontinuation). Symptomatic re-

mission is defined as having a score ≤ 3 on the PANSS items P1, P2, P3, N1, N4, N6, G5, and G9, maintained for at least 6 months [21]. Secondary efficacy endpoints included the time to symptomatic remission, proportion of patients who achieved combined symptomatic and functional remission, which was defined as symptomatic remission and Personal and Social Performance (PSP) score > 70, and changes in PANSS total score, Clinical Global Impression of Severity (CGI-S) score, Clinical Global Impression of Change (CGI-C) score, PSP total score from baseline to LOCF, and hospitalization and emergency room (ER) visits within 12 months prior to the start of PP3M and during follow-up. Safety endpoints included the proportion of patients who reported treatment-emergent adverse events (TEAE) and extrapyramidal symptoms rating scale (ESRS) score.

Statistical Analyses

The sample size for the REMISSIO study was calculated based on results from the pivotal non-inferiority study PSY-3011 [6,22]. Assuming 50% of the patients would achieve symptomatic remission and a study withdrawal rate of between 25% and 30%, 300 patients would be required to determine the proportion of patients who achieved symptomatic remission and for exploratory investigation of subgroups with a two-sided 95% CI for a single proportion.

The modified intent-to-treat (mITT) analysis set consisted of all patients who provided written consent and received at least one dose of the study medication. The mITT efficacy analysis set consisted of all patients from the mITT analysis set who had at least one post-baseline efficacy assessment. The mITT safety analysis set consisted of all patients from the mITT analysis set who had at least one post-baseline safety assessment.

Endpoint analysis using the LOCF method was performed in addition to observed case analysis. Actual values and changes from baseline were summarized descriptively at each assessment time point and at the patient's last evaluation (LOCF endpoint), including the 95% CI for efficacy outcomes. *p* values were not reported here given this was an exploratory study with no hypotheses-confirming objectives, and no adjustments were performed for multiplicity [23]. The time to symptomatic remission was estimated using the Kaplan–Meier method. The maintenance of efficacy was investigated using Schuirmann's

test to evaluate the change from baseline to LOCF end-point in PANSS total score, with a non-inferiority margin of five points on the PANSS scale. Missing PANSS item scores were imputed with the closest rounded integer to the average of the remaining items within the subscale (positive, negative, and general psychopathology) at the time point. No imputation was performed if more than

15% of the PANSS items were missing. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 305 patients were enrolled and received at

Table 1. Demographics and baseline characteristics (mITT analysis set)

Variable	Asian subgroup (n = 71)		South Korea (n = 33)		Malaysia (n = 21)		Taiwan (n = 17)		Overall study (n = 305)	
	Patient (n)	Value	Patient (n)	Value	Patient (n)	Value	Patient (n)	Value	Patient (n)	Value
Age (yr)	71	35.4 ± 7.8	33	34.9 ± 8.0	21	35.4 ± 8.2	17	36.4 ± 7.1	305	36.5 ± 8.0
Sex	71		33		21		17		305	
Male	38	53.5	16	48.5	13	61.9	9	52.9	200	65.6
Female	33	46.5	17	51.5	8	38.1	8	47.1	105	34.4
Baseline BMI (kg/m ²)	71	25.8 ± 3.8	33	25.7 ± 3.5	21	26.8 ± 4.0	17	24.9 ± 3.9	303	27.4 ± 5.2
Psychiatric history	71		33		21		17		305	
Years from start of first antipsychotic treatment to baseline visit	71	10.2 ± 6.6	33	10.2 ± 6.9	21	11.0 ± 6.6	17	9.3 ± 6.4	304	10.3 ± 7.2
Years from diagnosis of schizophrenia to baseline visit	71	9.5 ± 6.6	33	10.0 ± 6.8	21	11.1 ± 6.3	17	6.6 ± 6.1	304	9.2 ± 7.3
Hospitalization history	71		33		21		17		304	
Patients who have been hospitalized for psychiatric reasons	61	85.9	29	87.9	21	100	11	64.7	255	83.9
Years since first psychiatric hospitalization	60	8.1 ± 6.1	28	8.7 ± 6.0	21	7.9 ± 6.7	11	6.8 ± 5.4	254	8.9 ± 7.3
Total number of previous psychiatric hospitalization	61	3.0 ± 3.2	29	2.8 ± 2.2	21	3.2 ± 3.9	11	3.3 ± 4.0	255	3.3 ± 3.8
Suicidal ideation	71		33		21		17		305	
Patients who have attempted suicide since diagnosis	5	7	4	12.1	0	0	1	5.9	23	7.5
Previous treatment with PP1M	71		33		21		17		305	
Last PP1M dose category (mg)	71		33		21		17		305	
50	4	5.6	4	12.1	0	0	0	0	27	8.9
75	9	12.7	6	18.2	3	14.3	0	0	74	24.3
100	29	40.8	11	33.3	11	52.4	7	41.2	114	37.4
150	29	40.8	12	36.4	7	33.3	10	58.8	90	29.5
Patients who switched to PP1M from oral or injectable	68		32		21		15		299	
Oral	39	57.4	23	71.9	12	57.1	4	26.7	171	57.2
Injectable	29	42.6	9	28.1	9	42.9	11	73.3	128	42.8
Patients who switched to PP3M monotherapy from PP1M monotherapy	55	77.5	28	84.8	14	66.7	13	76.5	253	83.0
Patients who switched to PP3M polytherapy from PP1M polytherapy	16	22.5	5	15.2	7	33.3	4	23.5	52	17.0

Values are presented as mean ± standard deviation or number (%). Percentages were calculated based on the number of patients with available data. BMI, body mass index; mITT, modified intent-to-treat; PP1M, paliperidone palmitate 1-month formulation; PP3M, paliperidone palmitate 3-month formulation.

least one dose of PP3M (mITT analysis set). Of these, 71 (23.3%) were Asian (South Korea: 33, Malaysia: 21, Taiwan: 17) and 241 were non-Asian. All of the Asian patients and 234 non-Asian patients were treated with at least one dose of PP3M.

Study completion rates were similar across the Asian subgroup (95.8%) and overall study population (95.4%). Age, baseline body mass index, psychiatric and hospitalization history, and proportion of patients who have attempted suicide since diagnosis were consistent across the Asian subgroup and the overall study population (Table 1). Compared to other patient groups within the Asian subgroup, Taiwanese patients had less years (6.6 years) from diagnosis of schizophrenia to baseline visit; lower proportion of Taiwanese (64.7%) had been hospitalized for psychiatric reasons; and no Malaysian patients had attempted suicide since diagnosis. The sex distribution for the Asian subgroup and South Korean and Taiwanese patient groups was relatively well-balanced, whereas, 61.9% of Malaysian patients and 65.6% of the overall study population were male.

Prior to switching to PP3M treatment, the majority of Asian patients received 100 mg eq. or 150 mg eq. of PP1M; consistent with that in the overall study population (Table 1).

PP3M Treatment Exposure

The mean ± standard deviation (SD) duration of PP3M treatment (in days) was comparable across all groups (Asian subgroup: 261.7 ± 39.6, South Korea: 257.1 ± 48.9, Malaysia: 260.3 ± 39.0, Taiwan: 272.4 ± 5.1, overall population: 263.0 ± 42.5). The mean ± SD doses administered to patients across all groups were relatively consistent from Day 1 through to Month 9; the majority of Asian patients received 350 mg eq. followed by 525 mg eq., 263 mg eq., then 175 mg eq. (Fig. 1). The mean average ± SD dose administered during follow-up to Asian patients was 391.4 ± 114.0 mg eq. and that to the overall study population was 363.8 ± 116.0 mg eq.; within the Asian subgroup, 362.0 ± 128.6 mg eq., 391.7 ± 94.2 mg eq., and 447.8 ± 86.9 mg eq. were administered to South Korean, Malaysian, and Taiwanese patients, respectively. Amongst Asian patients, 5.6% had their PP3M dose decreased and 2.8% increased; while in the overall study population the proportions were 4.9% and 3.6%, respectively.

Efficacy

Symptomatic remission

The mITT efficacy analysis set included 303 subjects from the overall REMISSIO study with 70 of them being

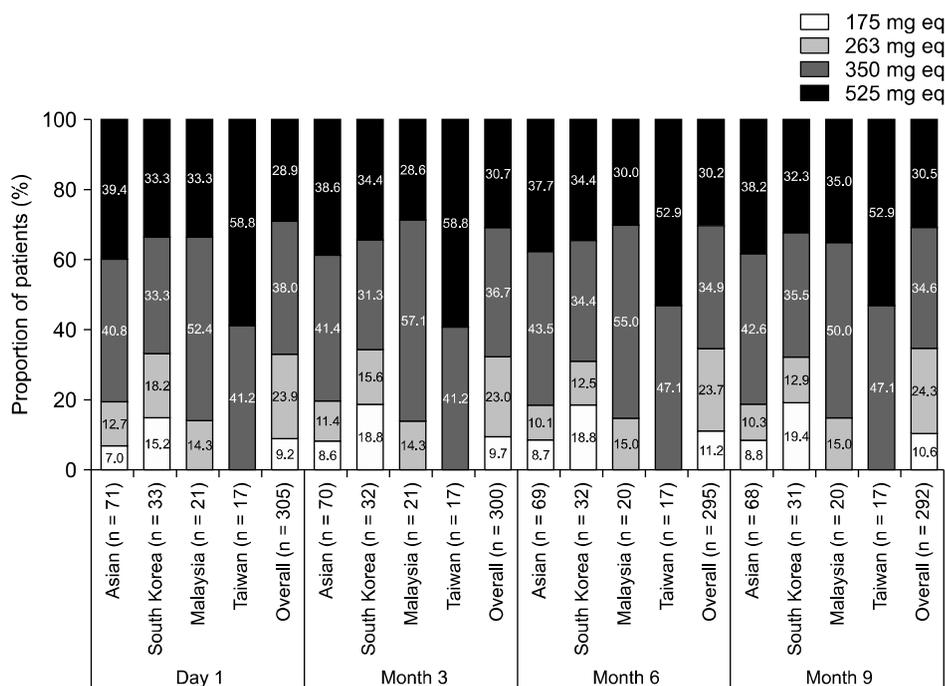


Fig. 1. PP3M treatment exposure over the 12-month treatment period (mITT efficacy analysis set). mg eq, milligram equivalents; mITT, modified intent-to-treat; PP3M, paliperidone palmitate 3-month formulation.

Table 2. Symptomatic remission rates during follow-up (mITT efficacy analysis set)

Time point	Asian subgroup (n = 70)		South Korea (n = 32)		Malaysia (n = 21)		Taiwan (n = 17)		Overall study (n = 303)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Month 6	46 (66.7)	54.3–77.6	21 (65.6)	46.8–81.4	13 (65.0)	40.8–84.6	12 (70.6)	44.0–89.7	148 (49.8)	44.0–55.7
Month 9	49 (71.0)	58.8–81.3	23 (71.9)	53.3–86.3	14 (70.0)	45.7–88.1	12 (70.6)	44.0–89.7	166 (56.7)	50.8–62.4
Month 12	50 (73.5)	61.4–83.5	23 (74.2)	55.4–88.1	15 (75.0)	50.9–91.3	12 (70.6)	44.0–89.7	171 (59.2)	53.3–64.9
LOCF	50 (71.4)	59.4–81.6	23 (71.9)	53.3–86.3	15 (71.4)	47.8–88.7	12 (70.6)	44.0–89.7	172 (56.8)	51.0–62.4

Percentages were calculated based on the number of patients with available data.
LOCF, last observation carried forward; mITT, modified intent-to-treat.

Table 3. Combined symptomatic and functional remission^a rates during follow-up (mITT efficacy analysis set)

Time point	Asian subgroup (n = 70)			South Korea (n = 32)			Malaysia (n = 21)			Taiwan (n = 17)			Overall study (n = 303)		
	Patient (n)	Total patients (N)	Data (%)	Patient (n)	Total patients (N)	Data (%)	Patient (n)	Total patients (N)	Data (%)	Patient (n)	Total patients (N)	Data (%)	Patient (n)	Total patients (N)	Data (%)
Month 6	28	69	40.6	15	32	46.9	9	20	45.0	4	17	23.5	80	297	26.9
Month 12	32	69	46.4	19	32	59.4	5	20	25.0	8	17	47.1	89	293	30.4
LOCF	32	68	47.1	19	31	61.3	5	20	25.0	8	17	47.1	92	289	31.8

Percentages were calculated based on the number of patients with available data.
LOCF, last observation carried forward; mITT, modified intent-to-treat.

^aDefined as symptomatic remission and Personal and Social Performance (PSP) score > 70.

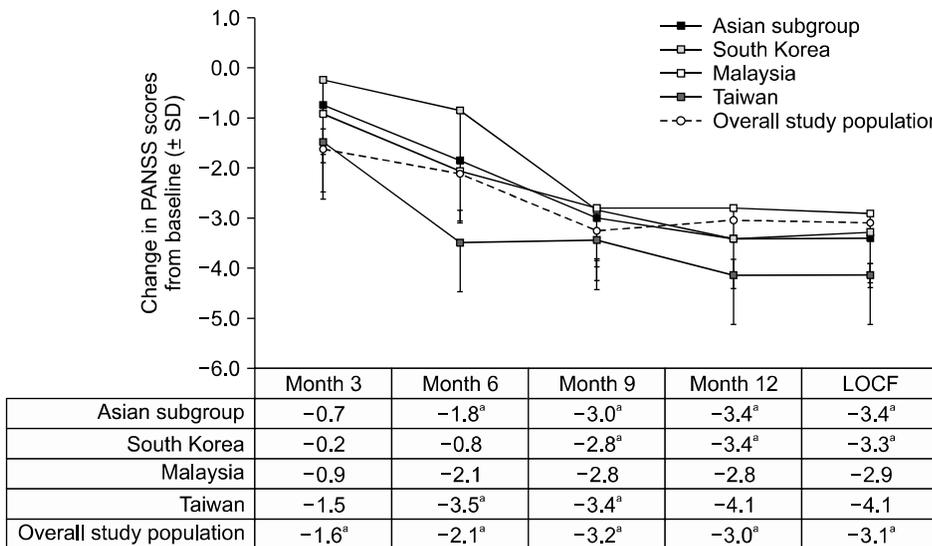


Fig. 2. Change from baseline in mean (SD) PANSS scores over the 12-month treatment period and at LOCF (mITT efficacy analysis set). LOCF, last observation carried forward; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation. ^aStatistically significant based on 95% confidence interval.

Asian patients. At LOCF, 71.4% of patients across the Asian subgroup achieved symptomatic remission compared with 56.8% for the overall study population; this observation was mirrored within the Asian subgroup (South Korea: 71.9%, Malaysia: 71.4%, Taiwan: 70.6%) (Table 2). The median (95% CI) time to symptomatic remission was 183 (179–186) and 247 (189–275) days in the Asian subgroup and overall study population, respec-

tively. Within the Asian subgroup, the median (95% CI) time to symptomatic remission was consistent [South Korea: 184 (176–258), Malaysia: 184 (176–268), Taiwan: 183 (179–Non-estimable (NE))].

Combined symptomatic and functional remission

At LOCF, combined symptomatic and functional remission rates were achieved in 47.1% of patients from the

Asian subgroup compared with 31.8% in the overall study population. Within the Asian subgroup, combined symptomatic and functional remission rates at LOCF ranged between 25% in Malaysian patients and 61.3% in South Korean patients (Table 3).

PANSS total score, CGI-S score, CGI-C, PSP total score

The mean ± SD PANSS total scores at baseline were similar across all groups (Asian subgroup: 44.8 ± 10.2, South Korea: 42.0 ± 8.7, Malaysia: 44.1 ± 9.0, Taiwan: 51.1 ± 12.0, overall population: 52.4 ± 10.6), indicating mild-moderate symptoms of schizophrenia. Statistically

significant reduction in mean ± SD PANSS total scores from baseline was observed at Month 6 (−1.8 ± 6.2; 95% CI: −3.3 to −0.4) through to LOCF in the Asian subgroup, and at Month 3 (−1.6 ± 5.4; 95% CI: −2.2 to 1.0) through to LOCF in the overall population (Fig. 2). Within the Asian subgroup, significant change in mean ± SD PANSS total scores from baseline was first observed at Month 6 (−3.5 ± 4.4; 95% CI: −5.7 to −1.2) through to Month 9 and at Month 9 (−2.8 ± 5.6; 95% CI: −4.9 to −0.8) through to LOCF in Taiwanese and South Korean patients, respectively.

The mean ± SD CGI-S scores at baseline were similar across all groups (Asian subgroup: 2.7 ± 0.9, South Korea:

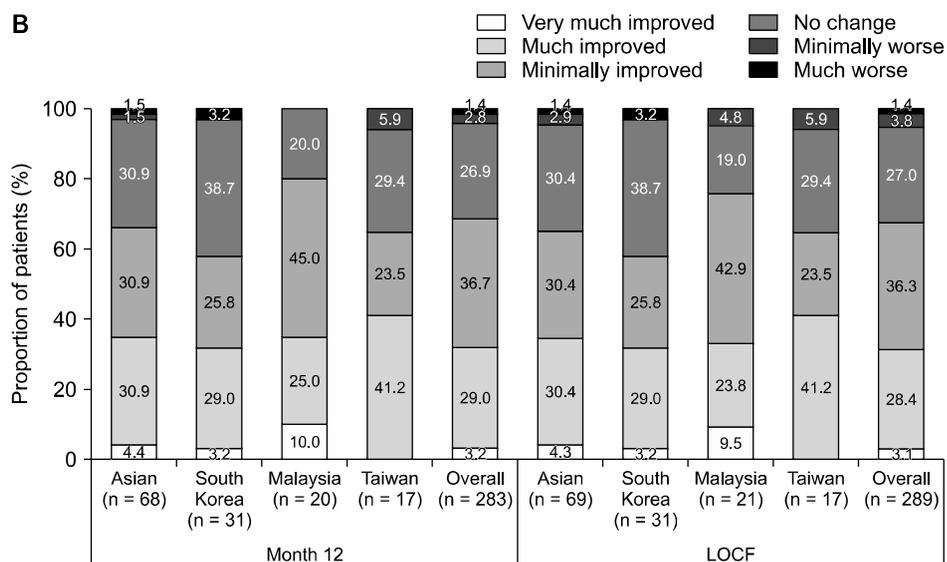
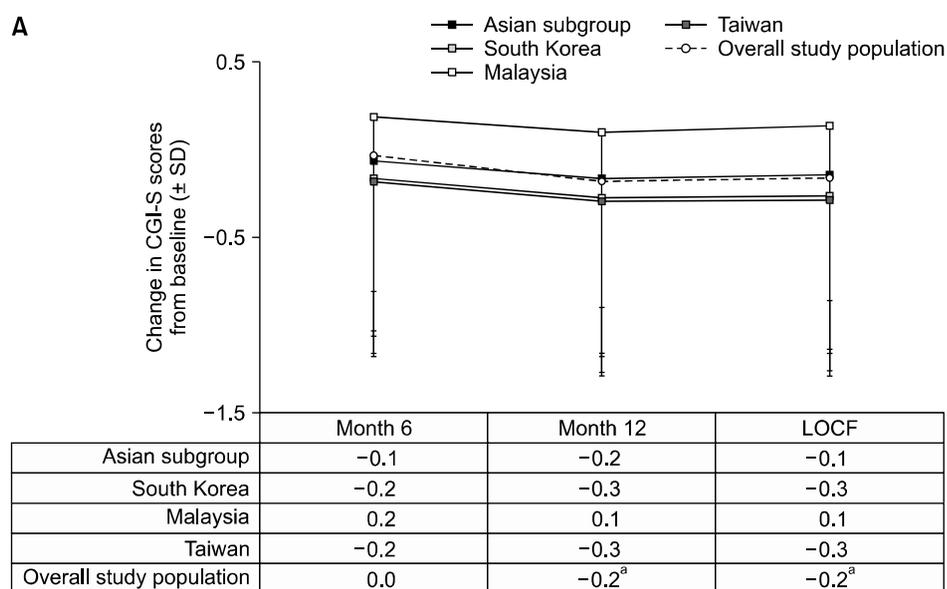


Fig. 3. Schizophrenia severity as assessed with CGI-S and CGI-C (mITT efficacy analysis set). (A) Change from baseline in mean (SD) CGI-S scores at Month 6, Month 12, and LOCF. (B) Proportion of patients with change in schizophrenia severity at Month 12 and LOCF. CGI-C, Clinical Global Impression of Change; CGI-S, Clinical Global Impression of Severity; LOCF, last observation carried forward; mITT, modified intent-to-treat; SD, standard deviation. ^aStatistically significant based on 95% confidence interval.

2.6 ± 0.9, Malaysia: 2.4 ± 1.1, Taiwan: 3.1 ± 0.5, overall population: 3.2 ± 1.0), indicating that patients were borderline-mildly ill. The trend in the change from baseline in mean ± SD CGI-S scores over time was similar across all groups (Fig. 3A). Despite patients having stable schizophrenia at study enrolment, improvement in schizophrenia severity as assessed with CGI-C was observed in 45/69 patients (65.2%) in the Asian subgroup and 196/289 patients (67.8%) in the overall study population at LOCF (Fig. 3B).

The mean ± SD PSP total scores at baseline were similar across all groups (Asian subgroup: 70.1 ± 12.5, South Korea: 72.6 ± 13.7, Malaysia: 72.3 ± 9.3, Taiwan: 62.8 ± 11.3, overall population: 65.9 ± 14.0). In the Asian subgroup, a statistically significant improvement in mean ± SD PSP scores from baseline was observed at Month 6 (2.1 ± 8.5; 95% CI: 0.1–4.2); a similar trend was observed in Taiwanese patients, with statistical significance maintained at Month 12 and LOCF (Table 4).

Hospitalization and ER visits

The proportion of patients with at least one psychiatric hospitalization during the 12 months before PP3M treatment was as follows: Asian subgroup: 12 (17.1%), South Korea: 8 (25.0%), Malaysia: 3 (14.3%), Taiwan: 1 (5.9%), overall population: 37 (12.2%). During follow-up, the proportion of patients with at least one psychiatric hospitalization in each group was lower as follows: Asian subgroup: 1 (1.4%), South Korea: 1 (3.1%), Malaysia: 0, Taiwan: 0, overall population: 8 (2.6%).

The proportion of patients with at least one ER visit during the 12 months before PP3M treatment was as follows: Asian subgroup: 4 (5.7%), South Korea: 2 (6.3%), Malaysia: 1 (4.8%), Taiwan: 1 (5.9%), overall population: 13 (4.2%). During follow-up, the proportion of patients with at least one ER visit in each group was as follows: Asian subgroup: 2 (2.8%), South Korea: 0, Malaysia: 0, Taiwan: 2 (11.1%), overall population: 4 (1.3%).

Safety

The overall incidence of TEAEs was 62.9% in the Asian subgroup and 53.1% in the overall study population (Table 5). Within the Asian subgroup, the overall incidence of TEAEs ranged between 38.1% in Malaysian patients and 82.4% in Taiwanese patients. The incidence of TEAEs considered possibly related to study medication

Table 4. Change from baseline in mean ± SD PSP total scores over the 12-month treatment period and at LOCF (mITT efficacy analysis set)

Time point	Asian subgroup (n = 70)			South Korea (n = 32)			Malaysia (n = 21)			Taiwan (n = 17)			Overall study (n = 303)		
	Number	Change from baseline	95% CI	Number	Change from baseline	95% CI	Number	Change from baseline	95% CI	Number	Change from baseline	95% CI	Number	Change from baseline	95% CI
Baseline	70			32			21			17			294		
Month 6	70	2.1 ± 8.5	0.1 to 4.2 ^a	32	2.6 ± 8.2	-0.4 to 5.6	21	-0.6 ± 9.1	-4.8 to 3.5	17	4.7 ± 7.6	0.8 to 8.6 ^a	289	0.7 ± 9.5	-0.4 to 1.8
Month 12	68	2.2 ± 12.4	-0.8 to 5.2	31	2.0 ± 13.6	-3.0 to 7.0	20	-2.8 ± 11.5	-8.1 to 2.6	17	8.5 ± 8.4	4.2 to 12.8 ^a	280	1.0 ± 11.4	-0.3 to 2.4
LOCF	70	2.0 ± 12.3	-0.9 to 5.0	32	1.9 ± 13.4	-2.9 to 6.8	21	-3.1 ± 11.3	-8.2 to 2.0	17	8.5 ± 8.4	4.2 to 12.8 ^a	294	1.0 ± 11.3	-0.3 to 2.3

Values are presented as mean ± standard deviation (SD).

LOCF, last observation carried forward; mITT, modified intent-to-treat; PSP, Personal and Social Performance.

^aStatistically significant based on 95% confidence interval (CI).

Table 5. Summary of TEAEs and TEAEs of interest (mITT safety analysis set)

Variables	Asian subgroup (n = 70)	South Korea (n = 32)	Malaysia (n = 21)	Taiwan (n = 17)	Overall study (n = 303)
TEAEs	44 (62.9)	22 (68.8)	8 (38.1)	14 (82.4)	161 (53.1)
Possibly related TEAEs	20 (28.6)	9 (28.1)	3 (14.3)	8 (47.1)	91 (30.0)
Serious TEAEs	5 (7.1)	4 (12.5)	0 (0)	1 (5.9)	18 (5.9)
TEAEs leading to treatment/study discontinuation	1 (1.4)	0 (0)	1 (4.8)	0 (0)	4 (1.3)
TEAEs in ≥ 5.0% of patients in either treatment group ^a					
Gastrointestinal disorders	10 (14.3)	4 (12.5)	2 (9.5)	4 (23.5)	21 (6.9)
General disorders and administration site conditions	7 (10.0)	4 (12.5)	1 (4.8)	2 (11.8)	26 (8.6)
Injection site pain	4 (5.7)	2 (6.3)	0 (0)	2 (11.8)	18 (5.9)
Infections and infestations	8 (11.4)	1 (3.1)	2 (9.5)	5 (29.4)	35 (11.6)
Injury, poisoning and procedural complications	4 (5.7)	2 (6.3)	1 (4.8)	1 (5.9)	11 (3.6)
Investigations	7 (10.0)	5 (15.6)	1 (4.8)	1 (5.9)	39 (12.9)
Weight increased	6 (8.6)	5 (15.6)	1 (4.8)	0 (0)	26 (8.6)
Nervous system disorders	20 (28.6)	12 (37.5)	1 (4.8)	7 (41.2)	47 (15.5)
Akathisia	5 (7.1)	3 (9.4)	0 (0)	2 (11.8)	11 (3.6)
Extrapyramidal disorder	4 (5.7)	0 (0)	0 (0)	4 (23.5)	4 (1.3)
Headache	4 (5.7)	4 (12.5)	0 (0)	0 (0)	7 (2.3)
Psychiatric disorders	19 (27.1)	9 (28.1)	3 (14.3)	7 (41.2)	58 (19.1)
Hallucination, auditory	5 (7.1)	2 (6.3)	1 (4.8)	2 (11.8)	7 (2.3)
Insomnia	8 (11.4)	3 (9.4)	1 (4.8)	4 (23.5)	11 (3.6)
Reproductive system and breast disorders	4 (5.7)	1 (3.1)	1 (4.8)	2 (11.8)	15 (5.0)
Respiratory, thoracic and mediastinal disorders	4 (5.7)	2 (6.3)	1 (4.8)	1 (5.9)	6 (2.0)

Values are presented as number (%). Percentages were calculated based on the number of patients with available data.

mITT, modified intent-to-treat; TEAE, treatment-emergent adverse event.

^aListed according to body systems and preferred terms (MedDRA version 20.0).

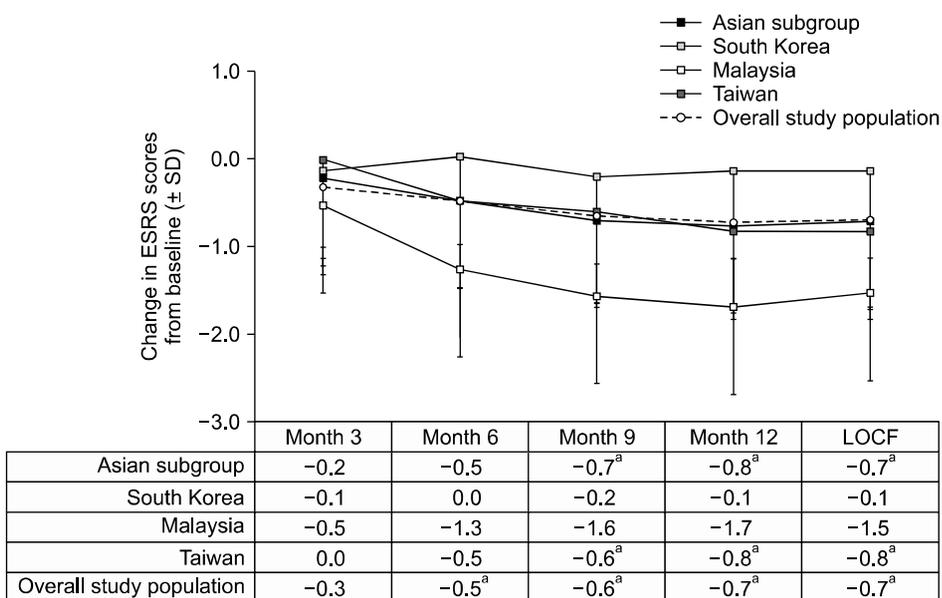


Fig. 4. Change from baseline in mean (SD) ESRS scores over the 12-month treatment period and at LOCF (mITT safety analysis set).

ESRS, Extrapyramidal Symptoms Rating Scale; LOCF, last observation carried forward; mITT, modified intent-to-treat; SD, standard deviation.

^aStatistically significant based on 95% confidence interval.

was similar in the Asian subgroup (28.6%) and overall study population (30.0%). Within the Asian subgroup, the incidence of TEAEs considered possibly related to study medication ranged between 14.3% in Malaysian patients

and 47.1% in Taiwanese patients. No deaths were reported in this study. Across all groups, the incidence of TEAEs leading to treatment or study discontinuation was low, and the most common TEAEs were related to the

nervous system or psychiatric disorders.

The trend in the change from baseline in ESRS scores over time was similar across all groups (Fig. 4). In the Asian subgroup, significant change in mean \pm SD ESRS scores from baseline was first observed at Month 9 (-0.7 ± 2.3 ; 95% CI: -1.2 to -0.1) and maintained at Month 12 and LOCF (Fig. 4); a similar trend was observed in Malaysian patients. In the overall study population, significant change in mean \pm SD ESRS scores from baseline was first observed at Month 6 (-0.5 ± 2.4 ; 95% CI: -0.8 to -0.2) and maintained at Month 6, 9, 12, and LOCF.

DISCUSSION

This study aimed to examine the long-term efficacy and safety of PP3M on Asian patients with stable schizophrenia in a naturalistic setting. Our findings showed that PP3M was efficacious and well-tolerated with a predictable safety profile in Asian patients with stable schizophrenia across a 12-month treatment period; consistent with findings from a largely non-Asian patient population.

Achieving complete symptomatic remission is a key challenge in the treatment of schizophrenia [24]. Our study showed that 71% of Asian patients achieved symptomatic remission with PP3M after 12 months of treatment. The numerically higher symptomatic remission rate in the Asian subgroup compared with that of the overall population at LOCF (57%) may be attributed to the difference in mean \pm SD PANSS total scores at baseline (Asian subgroup: 44.8 ± 10.2 vs. overall population: 52.4 ± 10.6). In another subgroup analysis involving East Asian patients (China, Japan, South Korea, and Taiwan), 50% achieved symptomatic remission after 48 weeks of treatment [25]. The primary study of the East Asian subgroup analysis included 26 countries across the Americas, East Asia, and Europe and showed that 58% of patients achieved symptomatic remission after 48 weeks of treatment [6]. Taken together, the symptomatic remission rate for the overall REMISSIO study population (57%) is consistent with those of previous PP3M studies (50–58%) [6,25]; while the symptomatic remission rate for the Asian subgroup (71%) in this naturalistic clinical setting, at the very least, does not appear to be worse than what was observed in the overall REMISSIO population or previous studies [6,25]. In comparison with patients who received second-generation oral antipsychotics, an earlier retro-

spective cohort study reported significantly higher remission rates in patients who received one-monthly paliperidone palmitate LAI (45% vs. 23%) [10].

Hospitalization rates have been used as an alternative measure for relapse [11,12]. Our study demonstrated a lower proportion of patients who had at least one psychiatric hospitalization after PP3M treatment (1%) than 12 months before PP3M treatment (17%). Our findings are consistent with findings from an East Asian subgroup analysis, where 3% of patients on PP3M had at least one psychiatric hospitalization during the 48-week study [25]. Our findings also corroborate with other studies that reported lower rates of relapse [14], risk of rehospitalization [15], and treatment failure as a result of psychiatric hospitalization with PP1M than with oral antipsychotics [16]. Taken together, these findings suggest that PP3M may reduce relapse of schizophrenia and psychiatric hospitalization.

Adherence to antipsychotic medications has shown to improve patients' quality of life [26] and treatment outcomes [27]. In our study, 95.8% of patients completed the 12-month treatment period. This result is relatively high for a long-term study on schizophrenia. By comparison, study completion rates in other PP3M studies were 83–84% [6,25] and that in RLAI studies ranged between 39% and 71% [28–31]. These are important findings as treatment discontinuation rates have been reported to be high amongst patients with schizophrenia. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study reported that over 70% of patients discontinued oral medications within 1.5 years as a result of medication-related factors such as adverse events and lack of perceived efficacy [32]. Importantly, non-adherence contributes to disease relapse [1,7,32], higher rates of psychiatric rehospitalization [2,10,33,34], and increased need for ER visits [33,34]. The high treatment completion rate in our study suggests good adherence, which may have translated to the high symptomatic remission rate (71%) and low hospitalization (1%) and ER visit rates (3%) after 12 months of PP3M treatment.

LAI formulations improve medication adherence in patients with schizophrenia, especially when compared with oral antipsychotics [35–37]—which have to be administered daily and, at times, more than once daily [38]. PP3M is a LAI administered once every 3 months for the treatment of schizophrenia, and is suitable for main-

tenance use in early or advanced stages of the disease [39]. Earlier studies of PP3M demonstrated non-inferiority to PP1M [6] and a significantly delayed time to relapse compared to placebo [18]. Evidence of PP3M efficacy is also supported by the low estimated number-needed-to-treat (95% CI) for relapse prevention at 12 months (3.4 [2.2–7.0]) [40].

Real-world studies of PP3M demonstrated improved outcomes for adherence [6,25], hospitalization visits [16,25] and cost-effectiveness [41,42] compared to other treatment modalities. PP3M has been reported to be well-tolerated in patients with schizophrenia [6,18,25]. In our study, the overall incidence of TEAEs related to study medication were comparable between Asian patients (29%) and the overall study population (30%); this finding is consistent with a subgroup analysis of East Asian patients [25] in which the incidence of serious TEAEs in the open-label (17 weeks) and double-blind (48 weeks) phases were consistently comparable between East Asian patients and the overall study population. Treatment discontinuation due to TEAEs was low (< 5%) across our study (1.3–1.4%) and previous studies of PP3M (0–4%) [6,18,25]. Good tolerability with PP3M is in line with the high treatment completion rates observed in our study.

Certain limitations apply to this subgroup analysis. Inherent to the design of the primary study that is open-label and single arm, our ability to draw definitive conclusions may be somewhat muted. Our study was also not powered to assess differences between ethnic subgroups; hence any differences among the Asian countries and with the overall study population should be interpreted with caution. Our study included three Asian countries (South Korea, Taiwan, and Malaysia) and may not be fully representative of the entire patient population across Asia. Nonetheless, the Asian subjects in our study accounted for almost 25% of the overall study population. To our knowledge, there is currently no long-term efficacy and safety data on the use of PP3M in Asian patients with stable schizophrenia in a naturalistic setting. Hence, this Asian subgroup analysis can serve as an important reference and inform on the safe and appropriate use of PP3M for Asian schizophrenia patients.

In conclusion, PP3M is the only known LAI antipsychotic that offers a 3-month window of stable plasma drug concentrations. Our findings demonstrated the efficacy and tolerability of PP3M in Asian patients with stable

schizophrenia over 12 months of treatment, that is consistent with the results from the primary multinational study. Our findings also provided insights on the transition of PP1M to PP3M in a naturalistic setting in Asia. PP3M, with its reduced need for frequent dosing, may potentially improve treatment adherence, psychiatric hospitalization, relapse and ER visits.

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■ Conflicts of Interest

YC was the investigator of the REMISSIO study, which was sponsored by Janssen Pharmaceutical Companies of Johnson and Johnson; YC reports no other conflict of interest. YKY was the investigator of the REMISSIO study, which was sponsored by Janssen Pharmaceutical Companies of Johnson and Johnson; YKY reports no other conflict of interest. AHS was the investigator of the REMISSIO study, which was sponsored by Janssen Pharmaceutical Companies of Johnson and Johnson; AHS reports no other conflict of interest. PB is a full-time employee of Janssen and holds stocks in Johnson and Johnson. WT is a full-time employee of Janssen Asia-Pacific and holds stocks in Janssen Asia-Pacific awarded as part of his total compensation package.

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