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ORIGINAL RESEARCH

Long-term efficacy and safety of paliperidone palmitate once-monthly in Chinese patients with recent-onset schizophrenia

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Background: The subgroup analysis of a primary study (NCT01051531) evaluated the effect of long-term paliperidone palmitate once-monthly (PP1M) therapy in Chinese patients with recent-onset schizophrenia responding unsatisfactorily to previous oral antipsychotics.

Patients and methods: This 18-month, open-label study consisted of 3 phases – screening (7 days), treatment (18 months) and end-of-study/withdrawal visit. All enrolled patients (18–50 years) received PP1M: 150 mg eq. (day 1), 100 mg eq. (day 8) followed by a once-monthly flexible dose (50, 75, 100 or 150 mg eq.). Efficacy and safety were assessed.

Results: Among the 118 enrolled Chinese patients, 68 completed the treatment (mean age: 25.6 years; male: 54.7%). A clinically meaningful change from baseline to day 548 was observed in Positive and Negative Syndrome scale (primary endpoint, mean [SD]: −15.3 [20.76]), Personal and Social Performance scale (15.9 [19.65]), Clinician Global Impression-schizophrenia score (−1.2 [1.54]) and Medication Satisfaction Questionnaire score (0.9 [1.73]). Commonly reported treatment-emergent adverse events (TEAEs) included insomnia (13.9%), injection-site pain (13.9%), upper respiratory tract infection (13.0%), restlessness (13.0%) and akathisia (13.0%). Serious TEAEs were reported in 9.3% patients with schizophrenia being most common (6.5%) and one death (suicide) was observed.

Conclusion: Efficacy of PP1M corroborate findings from earlier studies and no new safety concerns emerged in this Chinese subgroup of patients with schizophrenia.

Keywords: Chinese patients, long-acting injectable, maintenance therapy, paliperidone palmitate once-monthly, schizophrenia

Introduction

Schizophrenia, a mentally debilitating disease, is the leading cause of psychiatric disability in adults from China,[1] which results in considerable economic burden.[2] Approximately 40–60% of patients are partially or totally non-compliant to oral antipsychotic medication in less than a year of treatment.[3-5]Although second-generation oral antipsychotics demonstrate lower side-effects as compared with the first-generation, the issue of non-adherence still persists.[6,7] Poor medication adherence to oral antipsychotics is a primary predictor of relapse and hospitalizations.[8] High relapse rates are commonly observed among schizophrenia patients in the initial five years of diagnosis.[8,9] Some factors contributing to inadequate medication adherence include complex medication regimen, irregular daily routine leading to missed doses or clinician's lack of awareness on adherence.[10,11]

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Long-acting injectables (LAIs) were designed to overcome these issues of non-adherence by decreasing the dosing frequency and signaling the clinician in the event of non-adherence by regular patient contact.[12] The LAIs were previously recommended when there was poor medication adherence or symptom exacerbation or in maintenance phase of therapy.[13–15] The early phase of schizophrenia (initial 2 years up to 5 years) is an important period for intervention with implications on long-term prognosis to prevent schizophrenia-associated impairments and disabilities including relapse.[16] Recent guidelines recommend LAIs in all phases of schizophrenia including first-line therapy as well as the initial 2–5 years.[17–19]

Paliperidone palmitate once-monthly (PP1M) is an LAI with unique pharmacokinetics, wherein rapid therapeutic concentrations are attained post-initiation and the once-monthly dosing leads to sustained therapeutic effect. PP1M has been approved for the treatment of schizophrenia and schizoaffective disorder in various countries world-wide.[20] Studies have demonstrated efficacy and safety of PP1M in acute phase in schizophrenia patients from China,[21–23] albeit limited information is present on the long-term maintenance therapy with PP1M in this population.[24]

Cultural and ethnic variations in patients with schizophrenia have been widely acknowledged and are known to influence epidemiology, diagnosis, symptom expression and treatment outcomes.[25–27] Differences in acceptability to antipsychotics and variances in efficacy and tolerability profiles of antipsychotics among Chinese patients with schizophrenia have been corelated with pharmacodynamic and pharmacokinetic inconsistencies and are known to have clinically relevant implications on prescription patterns in China.[28,29] In addition, the influence of traditional herbal medicine, a prevalent practice in China and social stigma associated with psychiatric conditions, could potentially influence the course and outcomes of antipsychotic treatments.[26,30,31] The Chinese subgroup therefore represents a unique population with a high cultural impact. The primary study of the current subgroup analysis, a long-term, open-label, Phase 3b, Asia-Pacific (AP) study demonstrated significant clinical improvement and reduction in hospitalizations with PP1M therapy in patients who had recent-onset schizophrenia and had failed previous second-generation oral antipsychotics.[32] This analysis was carried out in the Chinese subgroup of schizophrenia patients from the primary study to identify long-term efficacy and safety of PP1M in this population.

Methods

Patients

This study included patients 18–50 years (both inclusive) of age, recently diagnosed (≤5 years) with schizophrenia (as per Diagnostic and Statistical Manual of Mental Disorders-4th edition [DSM-IV]). Detailed methodology of this study has been published previously.[32] Briefly, the key inclusion criterion was a history of unsuccessful treatment with oral antipsychotics and the key exclusion criterion was suspected psychiatric diagnosis due to drug abuse or medical conditions.

An Independent Ethics Committee or Institutional Review Board (all Independent Ethics Committees from China are listed in the Supplementary material) approved the study protocol at each study site. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before study enrollment.

Study drug

The doses of PP1M are expressed as milligram equivalent (mg eq.) wherein pharmacologically active paliperidone: 75, 100 and 150 mg eq. correspond to 117, 156 and 234 mg of paliperidone palmitate, respectively. PP1M injections were supplied as aqueous extended-release suspensions for intramuscular injections in pre-filled syringes.

Study design

The current study was a subgroup analysis of an 18-month, multicenter, single-arm, open-label study conducted across AP region between April 2010 and May 2013.[32] Briefly, the study consisted of a screening phase of up to 7 days, an open-label treatment phase of 18 month (day 1 to day 548) and an end-of-study or early-withdrawal visit. The patients were administered PP1M: 150 mg eq. on day 1, 100 mg eq. on day 8 (both in deltoid muscle) followed by flexible doses of 50, 75, 100 or 150 mg eq. once-monthly (deltoid or gluteal muscle) (Figure 1).

Concomitant medications

Continuation of mood-stabilizing agents, anti-depressants, benzodiazepines (used for at least three months before the study) and lorazepam (0.5 mg up to 6 mg/day) were allowed in an open-label manner. Anti-cholinergic medications could be continued up to 8 weeks before tapering off at the investigator's discretion.

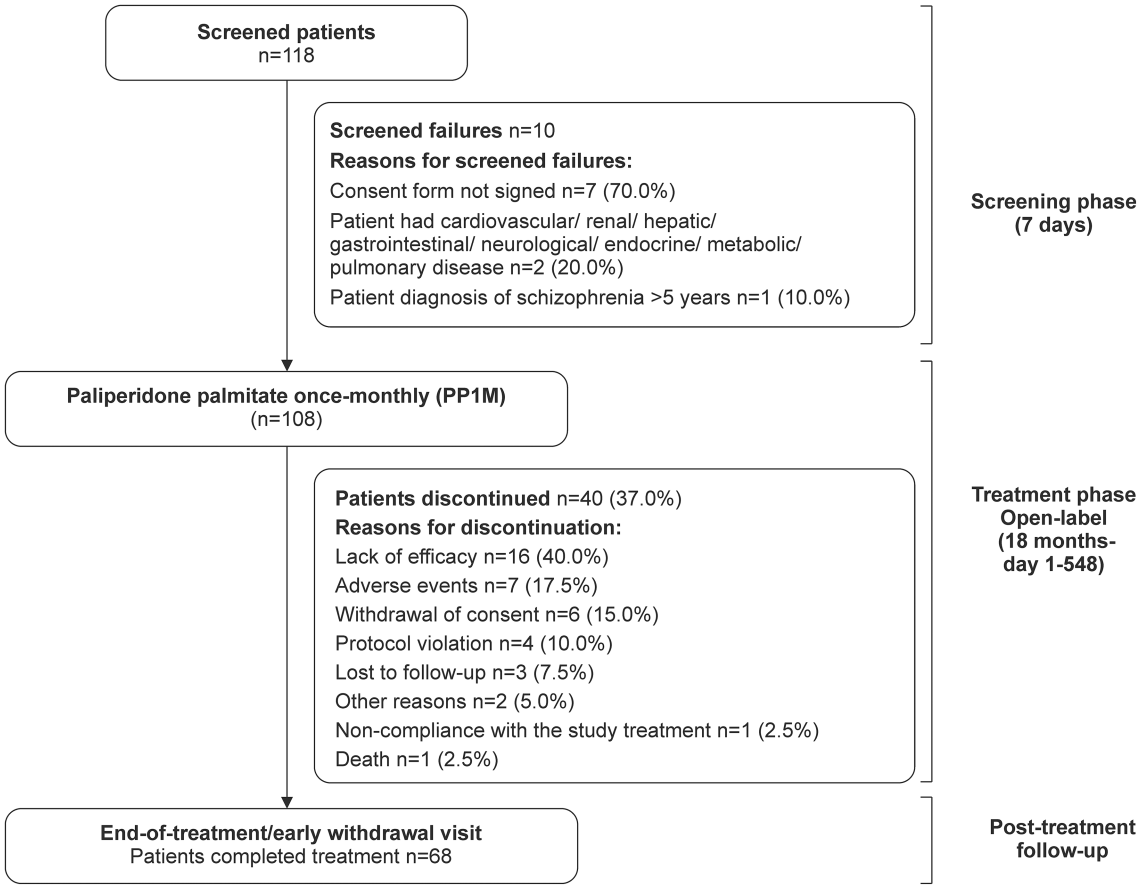

Figure 1 Study design and patient disposition.
Abbreviation: PP1M, paliperidone palmitate once-monthly.

Study outcomes

Efficacy assessments

The primary efficacy endpoint was change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to the end-of-study (day 548) after switching from oral antipsychotics to PP1M. Secondary endpoints included the changes from baseline to the end of study in Personal and Social Performance (PSP) scale score including evolution of ratio of mild degree of dysfunction (PSP total score 71–100), varying degree of difficulty (31–70) and poor level of function (≤30); PANSS five factor scores; improvement, worsening and stable conditions in PANSS total scores; response rates for PANSS total score; symptom remission; overall score in global severity of illness (Clinical Global Impression-Schizophrenia [CGI-SCH] scale); Medication Satisfaction Questionnaire (MSQ, 7-point categorical scale); rate of patient discontinuation; rate of patients hospitalized during the study; total number of institutionalizations; institutionalizations in the retrospective (12 months before the initiation of PP1M) and prospective period (12 months after the initiation of PP1M); and dosage of injection.

Safety assessments

Safety assessments included continuous monitoring of treatment-emergent adverse events (TEAEs), physical examinations, vital signs measurements, clinical laboratory tests, body weight and evaluation of CGI of Movement Severity scale.

Statistical analysis

Similar to the sample size calculation for the AP study,[32] to detect a difference of 3 units in the PANSS total score with 90% power, assuming a drop-out rate of 20%, a total of 587 patients were recruited. Since only 118 patients were expected to be enrolled in China, this subgroup analysis was not sufficiently powered. Hence, statistical tests were not performed, and the data are presented descriptively. The number of institutionalizations in the retrospective and prospective periods (day 1 to 6 months and day 1 to 12 months) were compared using the mirror-analysis method. Both primary and secondary efficacy analyses were performed on the intent-to-treat (ITT) population that included all the patients who received at least

one PP1M injection. The safety analysis set comprised of all patients in the ITT population.

Results

Patient disposition and characteristics

A total of 118 patients from China were enrolled in the study. Of the total ITT population (n=108), 68 patients (63.0%) completed the study. Among the discontinued patients (n=40), the most common reason for early termination from the study was the lack of efficacy (n=16) followed by TEAEs (n=7) and withdrawal of consent (n=6) (Figure 1). Among the patients who withdrew due to lack of efficacy, 68.8% withdrew without a schizophrenia-related TEAE.

Prior to study enrollment, this Chinese subgroup of patients were on oral antipsychotics, with risperidone, olanzapine, paliperidone and sulpiride being most commonly used (Table S1). The most frequent diagnosis was paranoid type schizophrenia (61.1%). The mean time since the first diagnosis of disease was 2.0 years and most of the patients (69.4%) were diagnosed within three years prior to study enrollment (Table 1). Concomitant medications were used by 75.9% patients and antipsychotics (50.9%) were reported as the most commonly administered agents followed by diazepines, oxazepines, thiazepines, oxepines (combined, 15.7%); indole derivatives (7.4%) and benzamides (5.6%). A mean (SD) of 14.7 (6.41) PP1M doses were administered over a period of 412.2 (196.42) days in this Chinese patient subgroup.

Table 1 Patient demographics and baseline characteristics (intent-to-treat population)

Characteristics	Chinese subgroup (n=108)
Age, years	
Mean (SD)	25.6 (7.24)
Sex, n (%)	
Male	62 (57.4)
Weight, kg	
Mean (SD)	66.7 (13.23)
Body mass index, kg/m^2	
Mean (SD)	23.7 (4.17)
Schizophrenia type (DSM-IV), n (%)	
Paranoid	66 (61.1)
Disorganized	4 (3.7)
Undifferentiated	31 (28.7)
Residual	7 (6.5)
Elapsed time since first diagnosis, years	
Mean (SD)	2.00 (1.56)
Time since first diagnosis, n (%)	
<3 years	75 (69.4)
≥3 years	33 (30.6)
PANSS baseline total score	
n	108
Mean (SD)	67.6 (18.44)
CGI-SCH baseline overall severity score, n (%)	
n	108
<5	73 (67.6)
≥5	35 (32.4)

Abbreviations: CGI-SCH, Clinical Global Impression of Schizophrenia; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-4th edition; PANSS, Positive and Negative Symptom Scale (for schizophrenia); SD, standard deviation.

Efficacy findings

Primary efficacy endpoint

At the end of treatment (day 548), a significant and clinically meaningful improvement from baseline in the PANSS total score was observed in these patients (mean [SD]: −15.3 [20.76], 95% CI=−19.3; −11.4) (Table 2).

Secondary efficacy endpoints

Significant and clinically meaningful improvements in the PSP total score, PANSS five factor scores, CGI-SCH four symptoms and overall severity scores and MSQ score from baseline to the end of treatment (day 548) were observed (Table 2). A considerable proportion of patients exhibited an improvement in the PANSS total score and symptom remission from baseline to day 548 (Table 2). Only 0.9% of patients who were in remission at baseline did not achieve symptom remission at day 548. Also, the percentage of patients achieving a response (≥30% improvement from baseline in the PANSS total score) increased with each successive visit (Table 2). Notably, the percentage of patients with hospitalization in this study was 7.4%. The Kaplan Meier estimates for institutionalization due to psychiatric reasons was 6.5% (Table 2). The mirror-analysis revealed that the percentage of patients institutionalized in the 12-month period post PP1M therapy was lower (ie, 6.5% as compared to 37%) than that in the retrospective period (Table 2).

Safety findings

In this study, 90.7% of patients experienced at least one TEAE, and 9.3% of patients experienced at least one serious TEAE (Table 3). The most common TEAEs (>2% patients)

Table 2 Efficacy parameters (LOCF; intent-to-treat population)

Parameters	Chinese population (n=108)
Primary efficacy parameter	
PANSS total score, mean (SD)	
Baseline	67.6 (18.44)
Change from baseline[a]	−15.3 (20.76)
95% CI	−19.3; −11.4
Secondary efficacy parameters	
PSP scores, mean (SD)	
Baseline	53.8 (16.03)
Change from baseline[a]	15.9 (19.65)
95% CI	12.1; 19.6
PANSS five factor scores, mean (SD)	
Negative symptoms	
Baseline	18.7 (6.77)
Change from baseline[a]	−4.3 (5.66)
95% CI	−5.4; −3.3
Positive symptoms	
Baseline	19.9 (7.50)
Change from baseline[a]	−5.1 (8.14)
95% CI	−6.7; −3.6
Disorganized thought	
Baseline	14.6 (4.91)
Change from baseline[a]	−3.1 (5.08)
95% CI	−4.0; −2.1
Uncontrolled hostility	
Baseline	7.2 (3.70)
Change from baseline[a]	−1.4 (4.34)
95% CI	−2.2; −0.6
Anxiety/depression	
Baseline	7.2 (2.67)
Change from baseline[a]	−1.4 (2.92)
95% CI	−2.0; −0.9
Improvement in PANSS score at day 548, n (%)	
Improved	62 (57.4)
Worsened	11 (10.2)
Neither improved nor worsened	35 (32.4)
Response rates[b], n (%)	
Day 38	39 (36.1)
Day 188	61 (56.5)
Day 368	64 (59.3)
Day 548	70 (64.8)
Symptom remission (baseline to day 548), n (%)	
No to Yes	42 (38.9)
Yes to No	1 (0.9)
Yes to Yes	32 (29.6)
No to No	33 (30.6)
CGI-SCH, mean (SD)	
Negative symptoms	
Baseline	3.3 (1.26)
Change from baseline[a]	−0.9 (1.11)
95% CI	−1.1; −0.6
Positive symptoms	
Baseline	3.2 (1.66)
Change from baseline[a]	−1.0 (1.95)
95% CI	−1.4; −0.7
Depressive symptoms	
Baseline	2.0 (1.09)
Change from baseline[a]	−0.5 (1.07)
95% CI	−0.7; −0.3
Cognitive symptoms	
Baseline	2.9 (1.09)
Change from baseline[a]	−0.8 (1.30)
95% CI	−1.0; −0.5
Overall severity	
Baseline	3.8 (1.15)
Change from baseline[a]	−1.2 (1.54)
95% CI	−1.5; −0.9
MSQ score, mean (SD)	
Baseline	4.2 (1.11)
Change from baseline[a]	0.9 (1.73)
95% CI	0.5; 1.2
Hospitalization, n (%)	
Any reason	8 (7.4)
95% CI	3.3; 14.1
Kaplan Meier estimates-institutionalization, n (%)	
Any reason	8 (7.4)
Psychiatric reason	7 (6.5)
Institutionalizations at different time points, n (%)	
Retrospective period	40 (37.0)
Day 1 to 6 month	6 (5.6)
Day 1 to 12 month	7 (6.5)
Dosage of third injection, n (%)	
75 mg eq.	45 (44.1)
100 mg eq.	40 (39.2)
150 mg eq.	17 (16.7)

Notes: [a]Change from baseline to day 548.
[b]Response was defined as ≥30% improvement in PANSS total scores from baseline.
Abbreviations: CI, Confidence interval; CGI-SCH, Clinical Global Impression of Schizophrenia; LOCF, last observation carried forward; MSQ, Medication Satisfaction Questionnaire; PANSS, Positive and Negative Symptom Scale (for schizophrenia); PSP, Personal and Social Performance; mg eq., milligram equivalent; SD, standard deviation.

Table 3 Summary of treatment-emergent adverse events (safety analysis set)

TEAEs	Chinese subgroup (n=108)
Patients with ≥1 TEAE, n (%)	98 (90.7)
Patients with ≥1 serious TEAE, n (%)	10 (9.3)
Schizophrenia	7 (6.5)
Death	1 (0.9)
TEAEs leading to, n (%)	
Discontinuation/early withdrawal	13 (12.0)
Discontinuation from study	14 (13.0)
TEAEs reported in >2% patients, n (%)	
Injection-site pain	15 (13.9)
Insomnia	15 (13.9)
Upper respiratory tract infection	14 (13.0)
Nasopharyngitis	12 (11.1)
Dizziness	12 (11.1)
Abnormal weight gain	10 (9.3)
Somnolence	10 (9.3)
Headache	9 (8.3)
Schizophrenia	8 (7.4)
Sleep disorder	8 (7.4)
Nausea	6 (5.6)
Fatigue	6 (5.6)
Respiratory, thoracic and mediastinal disorders	6 (5.6)
Diarrhea	5 (4.6)
Initial insomnia	5 (4.6)
Sinus arrhythmia	5 (4.6)
Vision blurred	5 (4.6)
Vomiting	5 (4.6)
Anxiety	4 (3.7)
Hallucination, auditory	4 (3.7)
Constipation	4 (3.7)
Increased appetite	4 (3.7)
Injury, poisoning and procedural complications	4 (3.7)
Psychotic disorder	3 (2.8)
Prolactin-related TEAEs, n (%)	**17 (15.7)**
Menstrual disorder	10 (9.3)
Amenorrhea	3 (2.8)
Menstruation delayed	3 (2.8)
Breast tenderness	1 (0.9)
Erectile dysfunction	1 (0.9)
Oligomenorrhea	1 (0.9)
Spermatorrhea	1 (0.9)
Glucose-related TEAEs, n (%)	**1 (0.9)**
Extrapyramidal symptom TEAEs ≥1%, n (%)	**45 (41.7)**
Akathisia	14 (13.0)
Restlessness	14 (13.0)
Tremor	10 (9.3)
Dystonia	4 (3.7)
Muscle tightness	3 (2.8)
Parkinsonism	3 (2.8)
Tardive dyskinesia	2 (1.9)
Mean (SD) change in body weight, kg	
n	50
Baseline	66.8 (13.82)
Change from baseline	4.3 (7.30)
Increase ≥7%, n (%)	21 (42)

Abbreviations: SD, standard deviation; TEAE, treatment-emergent adverse events.

included injection-site pain, insomnia, upper respiratory tract infection, nasopharyngitis and dizziness. The most commonly reported serious TEAE (≥5% patients) was schizophrenia exacerbation. One incidence of death (0.9%, 1/108) due to suicide was also observed in this subgroup and was not considered to be related to PP1M by the investigator. Thirteen patients had TEAEs that led to discontinuation from treatment or premature withdrawal, with the most common reason being worsening of schizophrenia. Also, TEAEs occurred more frequently in the first three months for the patients who tapered off prior antipsychotic medications during the study compared with patients without any concomitant use of antipsychotics (60.2% vs 17.6%). Incidence of depression, muscle rigidity, musculoskeletal stiffness and salivary hypersecretion were not observed in this study.

Prolactin-related TEAEs were reported in 15.7% patients and were more commonly reported in women (30.4%) than in men (4.8%). Menstrual disorder was the most common prolactin-related TEAE (9.3%). Glucose-related TEAEs were less frequently reported (0.9%) and extrapyramidal symptom (EPS) TEAEs were observed in 41.7% patients. The most common EPS TEAEs included akathisia, restlessness and tremor. A mean [SD] weight gain of 4.3 [7.30] kg from baseline was observed (Table 3) and an increase of ≥7% in body weight from baseline was observed in 42.0% patients. A significant reduction in CGI of Movement Severity score (mean [SD]: −0.2 [0.80], 95% CI: −0.4; −0.1) involving Parkinsonism was also observed. No clinically relevant changes in the vital signs were observed in this study.

Discussion

Patients from the AP region with recent-onset schizophrenia, who had failed previous oral antipsychotics, responded favorably to 18 months of PP1M therapy.[32] The current subgroup analysis of Chinese patients from the AP study also demonstrated improvements in symptoms (PANSS and PANSS five factor), function (PSP), clinical status (CGI-SCH) and medication satisfaction (MSQ) along with a decrease in the hospitalizations and institutionalizations in this longest study (18 months) carried out in this population. Overall, the efficacy endpoints improved in Chinese subgroup, similar to the total AP group.[32]

The data on hospitalizations and institutionalizations in the course of PP1M LAI therapy is limited.[33] Institutionalizations are also indicators for assessment of health care resource utilization. A mirror-design analysis,[32] that closely resembles the real-world scenario, was employed in the current study to understand the changes between institutionalizations in the retrospective period versus the prospective period post PP1M therapy. The institutionalizations reduced considerably in the 12-month period of therapy as compared with the retrospective period (37.0% vs 6.5%) in this study. Observations from the current study combined with data from other recent real-world observations in naturalistic clinical settings revealed very low rates of new hospitalization with 12-month PP1M therapy,[34] suggesting that a lowered direct health care cost may be expected as a benefit of long-term PP1M therapy.[35]

Previously, two separate studies were conducted with PP1M treatment in recent-onset schizophrenia patients from China with a therapy duration of 3 months[23] and 6 months.[24] A reduction in PANSS total score, improvement in PSP score and change in MSQ score from baseline was observed in the 3-month (mean [SD]; −30.9 [19.51], 19.3 [16.30] and 1.1 [1.6]), 6-month (−29.0 [18.77], 14.9 [15.04] and 0.8 [1.42]) and the current 18-month study (−15.3 [20.76], 15.9 [19.65] and 0.9 [1.73]).[23,24] This sustained pattern of evidence observed across the different durations of therapy with respect to efficacy and patient satisfaction, support the relevance of PP1M in the initiation and maintenance therapy of recent-onset schizophrenia in Chinese patients.

No new safety signals were observed in the Chinese subgroup. The increase in TEAE instances (32.1%, 51.3% and 90.7%) and weight gain (7.8%, 28.6% and 42.0%) in the 3-, 6- and 18-month study could be attributed possibly to the increased duration of therapy.[23,24] The EPS-related TEAEs were noted to have the highest occurrence among all TEAEs in the 3-, 6- and the current 18-month study.[22,28] Of note, the prolactin-related TEAEs (11.6% vs 15.7%) and glucose-related TEAEs (0.6% vs 0.9%) were comparable between the 6- and current 18-month study.[24] Although there was an increase in the occurrence of TEAEs in the current study, treatment satisfaction for PP1M therapy among patients was similar to the previous studies.[23,24] Death due to suicide was reported in one 19-year-old woman in the Chinese subgroup and the incident was not attributed to PP1M treatment by the investigator. It is estimated that 20% to 40% of individuals with schizophrenia have a lifetime risk of attempting suicide and as compared to the general population, individuals afflicted with schizophrenia have an 8.5-fold greater risk of suicide.[36–39] The prevalence pattern of schizophrenia and suicides due to schizophrenia has been observed to be unique in China and Chinese women are at a higher risk than men, a reverse of what is observed in other global populations. A high suicide rate of 6.8 per 1000 people per year has been reported among individuals with schizophrenia from China, with a relative risk of 23.8 (95% CI: 18.8; 30.2) in patients with schizophrenia versus those without.[26]

The current study was limited by the open-label nature of its design in that it may have influenced the patient-reported outcomes and clinician ratings of the patients. Additionally, due to the small sample size, the study was not sufficiently powered to perform statistical analysis. Hence, future studies with a larger sample size including placebo or active comparators (other LAIs or oral antipsychotics) could be conducted to confirm the long-term efficacy and safety findings. Treatment adherence is monitored closely during the course of a clinical trial; however, similar adherence may not be achieved in real world, long-term treatment.

Conclusion

To summarize, PP1M showed a consistent efficacy profile, corroborating the overall AP population and no new safety findings were observed in this subgroup of Chinese patients with schizophrenia who had previously failed oral antipsychotics. The number of patients hospitalized was notably low and the duration of hospitalization in these patients reduced following 18 months of treatment with PP1M.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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Supplementary material

List of institutional review boards and ethics committees from China

Country	IRB/EC Name	Site Name
China	The EC of Beijing University 6th Hospital	Beijing University 6th Hospital
China	The EC of Beijing Anding Hospital	Beijing Anding Hospital
China	The EC of Xijing Hospital of the Fourth Military Medical University	Xijing Hospital of the Fourth Military Medical University
China	The EC of Shanghai Mental Health Centre	Shanghai Mental Health Centre
China	The EC of Nanjing Brain Hospital	Nanjing Brain Hospital
China	The EC of The 3rd Affiliated Hospital, Sun Yansen University	The 3rd Affiliated Hospital, Sun Yansen University

Table S1 Antipsychotics taken by patients prior to study enrollment (Chinese subgroup)

Prior Antipsychotic	Chinese subgroup (n=108) n (%)
Risperidone	54 (50.0)
Olanzapine	12 (11.1)
Paliperidone	10 (9.3)
Sulpiride	7 (6.5)
Aripiprazole	6 (5.6)
Ziprasidone	6 (5.6)
Ziprasidone hydrochloride	3 (2.8)
Perphenazine	3 (2.8)
Quetiapine fumarate	2 (1.9)
Quetiapine	1 (0.9)
Trihexyphenidyl hydrochloride	1 (0.9)
Amisulpride	1 (0.9)
No prior antipsychotic	2 (1.9)