ORIGINAL RESEARCH

Safety and efficacy of paliperidone palmitate 1-month formulation in Chinese patients with schizophrenia: a 25-week, open-label, multicenter, Phase IV study

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Rationale: Long-acting injectable (LAI) paliperidone palmitate 1-month formulation (PP1M) has demonstrated acceptable tolerability and favorable clinical outcomes in Western and Asian patients with schizophrenia. Hence, analysis of the outcomes of long-term PP1M treatment specifically in Chinese patients is of interest.

Objective: The aim of this study is to evaluate the long-term safety and efficacy of PP1M treatment in Chinese patients with schizophrenia.

Methods: In this 25-week, open-label, Phase IV study, patients (18–65 years) diagnosed with schizophrenia and having a baseline Positive and Negative Syndrome Scale (PANSS) total score of 60–120 (inclusive) were enrolled. All patients received injections of PP1M 150 mg eq. (day 1) and 100 mg eq. (day 8), followed by a flexible once-monthly maintenance dosing (75, 100, or 150 mg eq.).

Results: Of the 353 patients, 234 (66.3%) completed the study treatment (mean age, 31.1 years; 52.7% men). The PANSS total score (primary end point) improved significantly over the 6-month treatment period (mean [standard deviation] change from baseline to end of treatment, −27.2 [18.30]; $P<0.0001$). The Clinical Global Impressions-Severity and Personal and Social Performance scores (secondary end points) also improved significantly ($P<0.0001$). At 6 months, PP1M had a positive impact on medication satisfaction, adherence, and increased preference for LAIs. Treatment-emergent adverse events (TEAEs) were reported by 181 (51.3%) patients (TEAEs ≥5%: extrapyramidal disorder [15.3%], akathisia [10.5%], blood prolactin increase [8.8%], insomnia [5.4%]). A total of 8 deaths were reported, including 4 completed suicides.

Conclusion: Long-term treatment with PP1M was efficacious, and no new safety concerns were identified in Chinese patients with schizophrenia. Overall, the results were comparable with observations from previous studies.

Keywords: Chinese, long-acting injectables, open-label, paliperidone palmitate, PANSS, schizophrenia

Introduction

Sustained symptomatic remission and prevention of relapses are key components of the pharmacotherapy of schizophrenia that positively impact treatment outcomes.[1–3] Medication nonadherence is regarded as the strongest determinant of psychotic relapses that in turn impose enormous occupational and social impediment and considerably increase the risk of suicidal behavior.[4–7] In Chinese patients with schizophrenia, the medication nonadherence rate is estimated to range from 20% to 38%.[8,9] Among several

other factors, poor medication compliance was reported to be the most important predictor of psychotic relapses in these patients.[9]

Long-acting injectable (LAI) antipsychotics have the advantage of simplified treatment regimen, steady drug delivery, and freedom from daily dosing compared to their oral counterparts.[10,11] LAIs also increase the feasibility of monitoring appointments for scheduled injections, enabling tracking of nonadherence.[11] Several clinical studies and meta-analyses have attributed LAIs with optimum control of symptoms, prevention of relapses, and reductions in rehospitalizations, likely through achieving improved medication adherence.[10,12–14] The atypical LAI, paliperidone palmitate 1-month formulation (PP1M), is approved for acute symptom control and maintenance treatment of schizophrenia in adults in most countries worldwide.[15,16] Although LAIs are most likely used in cases of failure of oral antipsychotic treatment, exacerbations of symptoms, and frequent relapses, the unique pharmacokinetic profile of PP1M supports initiation of PP1M even in acute cases of early psychosis.[11,15–17]

A large body of clinical data from global studies has substantiated the efficacy and acceptable tolerability of PP1M for short-term treatment of schizophrenia.[10,18–24] The efficacy of PP1M for acute treatment of schizophrenia in Chinese patients was demonstrated by 4 short-term (13-week) studies that reported PP1M to be well tolerated with similar safety findings as other populations.[17,25–27]

The benefits of long-term maintenance[28–31] and recurrence prevention[32] in global patient populations with schizophrenia have also been shown across a flexible dose range of 50–150 mg eq. Two recently published long-term studies demonstrated the favorable efficacy and safety of PP1M in patients from the Asia-Pacific region (Chinese patients: n=100 in each study).[33,34] The 18-month study of PP1M in patients with recent-onset schizophrenia also showed significant reduction in the number and duration of hospitalizations.[33] The second study was a global noninferiority study including patients from the People's Republic of China that compared efficacy of PP1M to the newer paliperidone palmitate 3-month formulation.[34] Both studies established the acceptable tolerability of PP1M for maintenance therapy of schizophrenia and did not raise any safety concern specific to the Asian population.

The present study was conducted in response to a request from the China Food and Drug Administration to collect clinical data for PP1M in 500 Chinese patients. Previous clinical studies from the Asia-Pacific region provided data for 200 Chinese patients.[33,34] Therefore, the aim of the present study is to evaluate the safety and efficacy of PP1M in routine clinical use over a 6-month treatment period in an additional 300 Chinese patients with recent-onset or chronic schizophrenia. The study also intends to explore outcomes that are close to real world such as treatment adherence and caregiver burden following treatment with PP1M in these patients.

Methods
Study design
This 25-week, multicenter, non-randomized, open-label, prospective Phase IV study was conducted between October 2013 and March 2015, across 13 centers in the People's Republic of China (ClinicalTrials.gov identifier: NCT01947803). The study was divided into a screening phase (up to 1 week), a treatment phase (25 weeks), and a follow-up phase (30 days). The study protocol and amendments were reviewed by an Independent Ethics Committee at each study site: The Second Xiangya Hospital of Central South University, Nanjing Brain Hospital, First Hospital of Shanxi Medical University, First Affiliated Hospital of Kunming Medical University, Tianjin Anding Hospital, Guangzhou Brain Hospital, Mental Health Center of Wuhan City, First Affiliated Hospital of Medical College of Xi'an Jiaotong University, The Sixth People's Hospital of Hebei Province, The First Hospital of Hebei Medical University, Mental Health Center of Xi'an City, Beijing Huilongguan Hospital, West China Hospital, and The First Affiliated Hospital of College of Medicine – Zhejiang University. All studies were conducted in compliance with the Declaration of Helsinki consistent with Good Clinical Practices and applicable regulatory requirements. Written informed consent was obtained from all patients before enrollment.

Patients
Men and women aged 18–65 years (inclusive), diagnosed with schizophrenia (according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision [DSM-IV-TR]), having a Positive and Negative Syndrome Scale (PANSS) total score between 60 and 120 (inclusive), and currently receiving treatment with or without any antipsychotic were eligible. Enrolled patients included those who experienced recurrent episodes and those experiencing first psychotic episode.

Key exclusion criteria included active DSM-IV-TR diagnosis other than schizophrenia, history of substance dependence within 6 months before screening, suicide attempt within 12 months before screening or being at an imminent risk of suicidal or violent behavior, history of

nonresponsiveness to risperidone or paliperidone, and prior treatment with clozapine for refractory schizophrenia.

Study treatments

Doses of PP1M given to the patients are expressed herein as mg eq. of paliperidone, the active fraction of PP1M.[19] During the treatment phase, eligible patients received deltoid injections of paliperidone palmitate 150 mg eq. on day 1 and 100 mg eq. on day 8 followed by a monthly flexible dosing (75, 100, or 150 mg eq.), based on patient's tolerability and/or efficacy, administered as either deltoid or gluteal injection. Patients without documented exposure to oral risperidone, paliperidone extended-release (ER), risperidone LAI, or PP1M were recommended for oral tolerability testing and received paliperidone ER (3–6 mg/day) or oral risperidone (1–3 mg/day) for 2–3 days during the screening phase.

Concomitant medications

Mood stabilizers or antidepressants (except nonselective or irreversible monoamine oxidase inhibitors, β-blockers, sedative hypnotics, and anticholinergic antiparkinsonian medications) were allowed. Benzodiazepines (≤10 consecutive days within 1 month) were permitted in cases of emergencies during the study. Use of lorazepam (≤6 mg/day orally) or any other equivalent short-acting benzodiazepine to control agitation, irritability, restlessness, and hostility was allowed. All antipsychotics other than PP1M were discontinued before initiation of study treatment on day 1. Any other psychoactive prescription medications, herbal agents, and over-the-counter drugs were not allowed during the treatment phase. Electroconvulsive therapy and transcranial magnetic stimulation were also prohibited during the course of this study.

Efficacy measures

The primary efficacy end point was changes in PANSS total score[35] from baseline to days 8, 36, 92, and 176. The secondary efficacy analysis included changes in Clinical Global Impressions-Severity (CGI-S) scores[36] and Personal and Social Performance (PSP) scores[37] from baseline to days 8, 36, 92, and 176. Medication satisfaction was evaluated based on changes from baseline to days 64 and 176 in Medication Satisfaction Questionnaire (MSQ) score. The MSQ was a single-item questionnaire that was offered to patients or caregivers who rated the treatment between 1 (extremely dissatisfied) and 7 (extremely satisfied).[38,39] Medication adherence was assessed using changes from baseline to days 64 and 176 in the 10-item questionnaire, Medication Adherence Rating Scale (MARS; total score <4 indicates nonadherence).[40,41]

The Attitude of Patient's Preference for LAI (APL) measure was used to evaluate patient's preference for LAI over oral antipsychotics and was calculated as the number and percentage of patients showing preference for either treatment and also investigated the reasons for preference. The Involvement Evaluation Questionnaire-31 (IEQ-31) was used to evaluate caregiver burden and was offered to all caregivers. Scoring was based on a 5-point Likert scale for 31 items on 4 dimensions (tension, supervision, worrying, and urging) and recorded during the previous 4 weeks as a recall period to assess caregiver consequences.[42]

Safety measures

Evaluations of safety and tolerability included incidence of treatment-emergent adverse events (TEAEs) and changes from baseline in extrapyramidal symptom (EPS) rating scales (Abnormal Involuntary Movement Scale [AIMS],[43] Barnes Akathisia Rating Scale [BARS],[44] and Simpson Angus Scale [SAS]),[45] Columbia-Suicide Severity Rating Scale (C-SSRS; included after protocol amendment), clinical laboratory tests (including prolactin measurements), vital signs measurements, 12-lead electrocardiograms (ECGs), and physical examinations.

Statistical analysis

No formal sample size calculation was performed. Assuming a dropout rate of 15% based on experiences from 2 previous clinical studies of PP1M, 353 patients were expected to be enrolled in this study.[33,34] This sample size provided ~95% chance of observing no less than 1% of incidence of TEAEs.

All efficacy analyses were performed on the full analysis set that included patients who received at least 1 injection of PP1M during the treatment phase and had at least 1 postbaseline efficacy assessment. The safety set that included patients who received at least 1 injection of PP1M during study duration was used for safety evaluations. IEQ-31 evaluation was performed on the pharmacoeconomic analysis set comprising caregivers for patients who received at least 1 injection of PP1M during the treatment phase and had at least 1 postbaseline evaluation. All efficacy end points were compared using paired *t*-test or Wilcoxon signed-rank test, at a 2-sided significance level of 5%, and no adjustments were made for multiplicity. Subgroup analyses based on disease duration (recent-onset schizophrenia: ≤5 years and chronic schizophrenia: >5 years of psychiatric history) were performed using analysis of covariance, and the values at baseline were used as covariates. The cut-off year for the

subgroups was fixed at 5 years based on evidence suggestive of functional deterioration and decline in antipsychotic treatment responses within the 5 years of first psychiatric diagnosis.[46–48] For all efficacy end points, the values and changes from baseline were summarized descriptively, and last observation carried forward data were used for missing data imputation. All safety measurements were summarized descriptively.

Results

Patient disposition and characteristics

A total of 403 patients were screened for eligibility of which 353 with mean (standard deviation, SD) age of 31.1 (10.52) years entered the treatment phase. The majority (68.6%, n=242) of patients had recent-onset schizophrenia (Table 1). The demographic characteristics were consistent across the 2 subgroups except mean (SD) body weight (64.0 [12.28] vs 66.3 [12.29] kg), body mass index (23.1 [3.80] vs 24.4 [3.95] kg/m^2), and age (28.3 [9.40] vs 37.2 [10.32] years) that were numerically lower in patients with psychiatric history of ≤5 years than those with history of >5 years. The baseline clinical characteristics were similar between the 2 subgroups. The commonly prescribed prior antipsychotic and concomitant medications included trihexyphenidyl hydrochloride (24.4%), risperidone (11.3%), paliperidone (8.2%), lorazepam (7.4%), and alprazolam (5.9%).

Of the 353 enrolled patients, 234 (66.3%) completed the treatment at day 176. The most common reasons for study discontinuation were withdrawal of consent (36 [10.2%]),

TEAEs (30 [8.5%]), and lack of efficacy (15 [4.2%]) (Figure 1). All patients were included in the safety set (100%), whereas the full analysis set had 345 (97.7%) patients and the pharmacoeconomic analysis set had 301 (85.3%) patients. Of the 234 patients who completed the 25-week study, 230 completed the follow-up period at day 206. The mean (SD) dose of PP1M (excluding the dose on day 1 and day 8) in the entire patient population was 118.7 (24.60) mg eq. (recent-onset subgroup, 117.3 [24.43]; chronic schizophrenia subgroup, 121.8 [24.82]) during the study.

Primary efficacy

A significant ($P<0.0001$) improvement in mean (SD) PANSS total score was observed from baseline to day 8 (−5.8 [7.97]), day 36 (−13.9 [13.02]), day 92 (−21.5 [16.46]), and day 176 (end of the 6-month treatment period; −27.2 [18.30]) (Table 2). The subgroup analyses revealed that the magnitude of reductions in PANSS total scores was greater in patients with psychiatric history of ≤5 years as compared with those with a history of >5 years at all time points measured (Table 2).

Secondary efficacy

Significant ($P<0.0001$) changes in mean (SD) CGI-S scores from baseline on day 8 (−0.2 [0.55]), day 36 (−0.7 [0.88]), day 92 (−1.2 [1.06]), and day 176 (−1.6 [1.22]) were observed (Table 2). Mean (SD) changes in PSP scores also showed significant improvement on day 8 (3.3 [7.26]), day 36 (7.4 [10.24]), day 92 (11.0 [13.09]), and day 176 (14.9 [15.04])

Table 1 Demographic and baseline characteristics (safety set)

Characteristics	Psychiatric history of ≤5 years (N=242)	Psychiatric history of >5 years (N=111)	Total (N=353)
Age, mean (SD) (years)	28.3 (9.40)	37.2 (10.32)	31.1 (10.52)
Sex, n (%)			
Men	130 (53.7)	56 (50.5)	186 (52.7)
Body weight, mean (SD) (kg)	64.0 (12.28)	66.3 (12.29)	64.8 (12.31)
BMI, mean (SD) (kg/m^2)	23.1 (3.80)	24.4 (3.95)	23.5 (3.89)
Age at schizophrenia diagnosis, mean (SD) (years)	27.2 (9.58)	26.5 (8.78)	27.0 (9.33)
Number of prior institutionalizations[a], n (%)			
None	125 (52.7)	65 (60.7)	190 (55.2)
Once	92 (38.8)	31 (29.0)	123 (35.8)
Twice	18 (7.6)	11 (10.3)	29 (8.4)
Thrice	2 (0.8)	0	2 (0.6)
Suicide attempted, n (%)			
Yes, ≥1 year before the study entry	5 (2.1)	4 (3.6)	9 (2.5)
Baseline PANSS total score, mean (SD)	85.3 (13.55)	84.2 (12.86)	84.9 (13.33)
Baseline CGI-S score, mean (SD)	4.8 (0.84)	4.9 (0.81)	4.9 (0.83)
Baseline PSP score, mean (SD)	51.9 (14.14)	51.5 (13.28)	51.8 (13.86)

Note: [a]Number of prior institutionalizations in the last 12 months due to schizophrenia.
Abbreviations: BMI, body mass index; CGI-S, Clinical Global Impressions-Severity; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale.
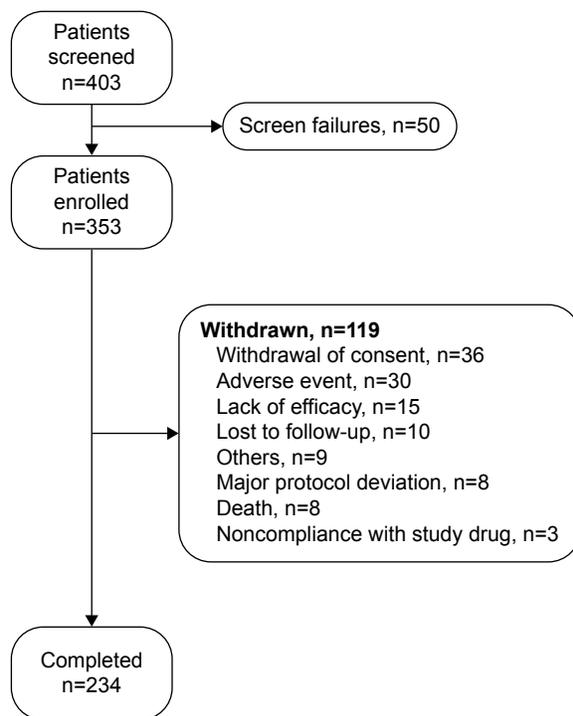
Figure 1 Patient disposition.

(*P*<0.0001). Clinically meaningful and significant changes in mean (SD) MSQ scores on day 64 (0.6 [1.51], *P*<0.0001) and day 176 (0.8 [1.62], *P*<0.0001) represented treatment satisfaction among patients. Subgroup analysis did not indicate any significant differences in the extent of improvement

for CGI-S, PSP, and MSQ scores between patients with a psychiatric history of ≤5 and >5 years.

Improved medication adherence was observed as indicated by significant mean (SD) changes from baseline in MARS scores on day 64 (1.7 [3.06], *P*<0.0001) and day 176 (2.2 [3.28], *P*<0.0001). Overall, the treatment adherence rate for all medications increased from 46.9% at baseline to 75.0% on day 64 and 82.3% on day 176 (Table 3). Based on the APL, the percentage of patients preferring LAI over oral antipsychotics was greater consistently throughout the study: 70.4% (baseline), 79.2% (day 64), and 76.9% (day 176) (Table 3). Among patients preferring LAIs, >70% favored deltoid injections over gluteal injections at all investigated study points. The reasons for this preference were simpler procedure and less embarrassment than receiving gluteal injections. A smaller proportion of patients preferred gluteal injections and claimed that these were less painful and simpler than deltoid injections. Simplified regimen, freedom from taking oral antipsychotics, and better symptom remission were among the top reasons for the higher preference toward LAIs. Significant (*P*<0.0001) mean (SD) reduction from baseline (31.8 [15.52]) in IEQ-31 scores was observed on day 64 (−6.7 [14.30]) and day 176 (−8.2 [15.84]), indicating meaningful relief in caregiver burden. Lowering of caregiver burden was significant (*P*<0.0001) for both subgroups on day 176 (psychiatric history of ≤5 years, −8.6 [16.98]; psychiatric history of >5 years, −7.2 [13.01]).

Table 2 Changes from baseline in primary efficacy scores (full analysis set; LOCF)

Efficacy measure	Mean (SD) change from baseline			*P*-value[a]
	Psychiatric history of ≤5 years (N=235)	Psychiatric history of >5 years (N=110)	Total (N=345)	
PANSS total score				
Day 8	−6.3 (8.06)	−4.9 (7.70)[b]	−5.8 (7.97)[c,d]	0.1659
Day 36	−15.3 (13.15)	−10.9 (12.26)	−13.9 (13.02)[c]	0.0044
Day 92	−23.2 (16.92)	−18.0 (14.89)	−21.5 (16.46)[c]	0.0067
Day 176	−29.0 (18.77)	−23.4 (16.70)	−27.2 (18.30)[e]	0.0085
CGI-S scores				
Day 8	−0.2 (0.51)	−0.2 (0.62)[b]	−0.2 (0.55)[c,d]	0.5794
Day 36	−0.7 (0.88)	−0.6 (0.89)	−0.7 (0.88)[c]	0.1952
Day 92	−1.2 (1.03)	−1.1 (1.10)	−1.2 (1.06)[c]	0.1123
Day 176	−1.6 (1.28)	−1.4 (1.09)	−1.6 (1.22)[c]	0.0686
PSP scores				
Day 8	3.2 (6.68)	3.4 (8.42)[b]	3.3 (7.26)[c,d]	0.9569
Day 36	7.5 (10.42)	7.3 (9.89)	7.4 (10.24)[c]	0.7592
Day 92	11.5 (13.33)	10.1 (12.55)	11.0 (13.09)[c]	0.2009
Day 176	15.4 (15.66)	13.9 (13.65)	14.9 (15.04)[c]	0.2215

Notes: [a]*P*-value was based on the analysis of covariance between subgroups (psychiatric history: ≤5 years and ≥5 years), with baseline value as the covariate. [b]n=109. [c]*P*<0.0001, Wilcoxon signed-rank test on change from baseline. [d]n=344. [e]*P*<0.0001, paired *t*-test on change from baseline.
Abbreviations: CGI-S, Clinical Global Impressions-Severity; LOCF, last observation carried forward; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale.

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Table 3 Changes in MSQ scores, MARS scores, and APL from baseline (full analysis set)

	PP1M (N=345)		
	Baseline	Day 64	Day 176
Change in MSQ score, mean (SD)	4.4 (1.29)	0.6 (1.51)	0.8 (1.62)
P-value[a]		<0.0001	<0.0001
Change in MARS score, mean (SD)	4.4 (2.88)	1.7 (3.06)	2.2 (3.28)
P-value[a]		<0.0001	<0.0001
Medication adherence rate (%)	46.9	75.0	82.3
Changes in APL measure			
Patients preferring LAI, n (%)	238 (70.4)	236 (79.2)	193 (76.9)
Injection-site preference, n (%)			
Deltoid	249 (73.9)	225 (75.3)	184 (73.3)
Gluteal	88 (26.1)	74 (24.7)	67 (26.7)

Note: [a]Wilcoxon signed-rank test on change from baseline.
Abbreviations: APL, Attitude of Patient's Preference for LAI; LAI, long-acting injectable; MARS, Medication Adherence Rating Scale; MSQ, Medication Satisfaction Questionnaire; PP1M, paliperidone palmitate 1-month formulation.

Safety

Overall, 181 (51.3%) patients experienced TEAEs during the study. The most frequently reported TEAEs (in ≥5% patients) were extrapyramidal disorder (54 [15.3%]), akathisia (37 [10.5%]), blood prolactin increase (31 [8.8%]), and insomnia (19 [5.4%]) (Table 4). The majority of TEAEs were rated as mild or moderate. There were 24 (6.8%) serious TEAEs; exacerbation of psychotic symptoms (11 [3.1%]) was the most common serious TEAE. In total, 31 (8.8%) patients prematurely discontinued the study due to TEAEs; worsening of schizophrenia (10 [2.8%]) was the most frequent TEAE responsible for discontinuation. In all, 96 (27.2%) patients experienced EPS-related TEAEs. Extrapyramidal disorder (54 [15.3%]), akathisia (37 [10.5%]), restlessness (3 [0.8%]), musculoskeletal stiffness (3 [0.8%]), Parkinsonism (2 [0.6%]), and tremor (2 [0.6%]) were the common (n≥2) EPS events. Changes in EPS-rating scales (AIMS/BARS/SAS) indicated that >90% of patients had normal movements (severity of abnormal movement = none) throughout the study (based on AIMS assessment of severity of dyskinesia) and that the majority (≥75%) of patients had no akathisia, and none reported severe akathisia throughout the study (BARS scores). No trend suggestive of Parkinsonism was identified throughout the study as indicated by the median SAS total score (0.00) at the end of treatment phase. Prolactin-related TEAEs were experienced by 41 (11.6%) patients, and the more common (n≥3) events included increased blood prolactin levels (31 [8.8%]), amenorrhea, menstrual disorder, and galactorrhea (3 [0.8%] each). Glucose-related TEAEs (blood glucose increase) were

Table 4 Treatment-emergent adverse events experienced by at least 1% of patients (safety set)

	PP1M (N=353), n (%)
Patients with TEAEs	181 (51.3)
TEAEs leading to drug withdrawal	31 (8.8)
Patients with ≥1 serious TEAE	24 (6.8)
Deaths	8 (2.3)
Completed suicides	4 (1.1)
Suicide attempt	3 (0.8)
TEAEs reported in ≥1% patients	
Insomnia	19 (5.4)
Body weight gain	14 (4.0)
Schizophrenia	13 (3.7)
Upper respiratory tract infection	8 (2.3)
Hepatic function abnormal	6 (1.7)
Palpitations	6 (1.7)
Transaminases increase	6 (1.7)
Poor quality sleep	5 (1.4)
Sleep disorder	5 (1.4)
Asthenia	5 (1.4)
Dizziness	4 (1.1)
Blood triglycerides increase	4 (1.1)
Impulsive behavior	4 (1.1)
Constipation	4 (1.1)
Vision blurred	4 (1.1)
EPS-related TEAEs	96 (27.2)
Extrapyramidal disorder	54 (15.3)
Akathisia	37 (10.5)
Prolactin-related TEAEs	41 (11.6)
Blood prolactin increase	31 (8.8)

Abbreviations: EPS, extrapyramidal symptom; PP1M, paliperidone palmitate 1-month formulation; TEAE, treatment-emergent adverse event.

reported in 2 (0.6%) patients. Clinically relevant weight gain (>7% increase in body weight) was reported in 28.6% of patients at the end of the follow-up period (day 206). Post-baseline changes in hematological parameters, vital signs, or ECGs were not clinically meaningful.

Deaths were reported in 8 (2.3%) patients (completed suicide, n=4; deaths, n=2; unexplained deaths, n=2). One of the 2 deaths was reported as a "sudden cardiac death" since the autopsy results did not find any other cause for the death, such as trauma or poisoning. However, the consideration of the death as a "sudden cardiac death" was speculative as the death was not witnessed and no ECG monitoring was performed. The reason for the second death (found dead in river) was not reported; however, the possibility of a suicide could not be ruled out. Patients who died were in the age group of 22–45 years (completed suicides, 22–45 years; other deaths, 30–43 years); mostly women (completed suicides: men =2, women =2; other deaths: men =1, women =3) and 6 of the 8 patients had a psychiatric history of >5 years (completed suicides and other deaths, n=3 each). As compared with

patients who survived (n=345), the patients who died had a longer duration of schizophrenia (mean [SD] duration, 4.6 [5.79] vs 7.5 [4.92] years). The mean (SD) MARS total score at baseline was 4.6 (2.26) in patients who died (n=8) and 4.3 (2.89) in patients who survived (n=341). Among the suicidal events, 2 of 3 suicide attempters and 2 of 4 suicide completers were women, and all 7 events occurred in younger patients (19–45 years). Two of the 4 suicide completers had documented prior nonfatal suicide attempt, and recent hospital admissions were reported in 3 of the 4 fatal suicide cases.

A protocol amendment was initiated to collect additional safety data, to include suicide risk evaluation (C-SSRS) and additional 12-lead ECG examination at all weekly visits (in addition to baseline and day 176 assessments, up to day 206 of the follow-up). After the amendment, evaluation of suicide risk based on C-SSRS scores was conducted in 28 of 353 patients. There were no reported suicidal attempts or completed suicides after amendment. No clinically notable cardiovascular abnormalities were observed based on additional ECG assessments.

Discussion

The present study evaluated the long-term safety and efficacy of PP1M in a large population of Chinese patients (n=353) with schizophrenia. In contrast to randomized controlled trials, the patient sample included in this study was representative of patients treated in everyday clinical practice, thus improving the external validity of these results. In addition, this study was designed to simulate real-world clinical situations in which patients are treated with flexible dosing of PP1M and evaluate pragmatic outcomes that potentially predict treatment responses. To our knowledge, such findings have not been reported earlier in a Chinese population with schizophrenia.

The efficacy findings from this study demonstrated that monthly flexible dosing (75, 100, or 150 mg eq.) of PP1M over a period of 25 weeks achieved favorable and significant (*P*=0.0001) reductions from baseline in the PANSS total scores (primary efficacy measure) for both total population and subgroups (patients with psychiatric history of ≤5 years and >5 years). Significant improvements in secondary efficacy end points, CGI-S and PSP scores, indicated progressive treatment response and improvements in psychosocial functioning in these patients.

Overall, PP1M showed greater symptom improvement in patients with recent-onset schizophrenia (psychiatric history of ≤5 years). This finding adds to available evidence that

values the use of PP1M treatment in early schizophrenia, challenging the practice of reserving LAIs for chronic cases and treatment failures.[17,48,49] The efficacy findings from this study are consistent with the outcomes from earlier global studies of PP1M and studies in Asian patients with schizophrenia.[21,22,25,27,31,33]

The safety findings from this study also corroborated the outcomes reported in other studies of PP1M in patients from the Asia-Pacific region.[17,25–27] The rates of TEAEs (51.3%) reported herein were consistent with the results of 2 long-term studies of PP1M in patients from the Asia-Pacific region (66.0% and 82.3%)[33,34] and global studies of PP1M,[30,31,50,51] and were comparable with the TEAE rates generally observed with oral atypical antipsychotic treatment (64%–70%).[52] Worsening of schizophrenia (2.8%) was the most common TEAE that led to treatment discontinuation.

The clinical benefits of PP1M with regard to treatment satisfaction (MSQ scores), adherence to antipsychotic medications (MARS), and preference for LAI treatments over oral equivalents (APL) were also demonstrated by this study. These efficacy measures are indicators of antipsychotic treatment success in the real world that impact long-term management of schizophrenia, ultimately achieving prevention of relapses and reductions in hospitalizations.[4,11,53] Several studies have regarded positive patient attitude as a key outcome driver and a reliable predictor of treatment acceptance that favorably impacts long-term medication adherence and clinical responses.[54–59] Improved patient satisfaction and positive attitude toward LAIs have been considered as important attributes that influence treatment choice among physicians.[54,56] In the present study, a higher number of patients preferred LAIs throughout the course of the 6-month treatment with PP1M. These results, along with data from a systematic review that observed a greater preference for LAIs among patients previously treated with LAIs versus LAI-naïve patients, represent a progressive trend and changing attitude towards LAIs among patients, as well as prescribing physicians.[55,59] The higher patient preference for deltoid over gluteal injections noted in this study is consistent with results from other reports, although gluteal injections have been associated with better tolerability.[50,54] Thus, the flexibility of PP1M administration as both deltoid and gluteal injections offers an additional advantage. These results add to the current knowledge about patient and physician experiences that favor the use of LAI antipsychotics in routine clinical practice at different stages of schizophrenia.[54,60,61]

A significant reduction in the magnitude of caregiver burden following the 6-month treatment with PP1M was also

observed. Alleviations in caregiver burden reflect meaningful changes in various aspects of life such as social functioning, personal relationships, daily routine activities, leisure, and physical and mental health, all suggestive of improving the quality of life. In most cases, family members are the caregivers, and reducing the burden positively influences their role in offering intensive patient support and care and ensuring treatment adherence.[62,63]

A total of 8 deaths were reported in the present study, and half of those deaths were reportedly due to suicide. A greater risk of suicidality has been observed in patients with psychiatric illness as compared with the general population, with the estimates for lifetime risk of suicide attempt ranging from 1% to 4.7% in the non-afflicted population, escalating to 5%–22% in patients with schizophrenia.[64–67] The prevalence of schizophrenia in the People's Republic of China is generally similar to that of Western and other Asian populations; however, there are some different demographic and sociocultural risk factors for suicide in China. For example, in rural China, women are considered to be at greater risk than men for suicide.[68–71]

Some common predictors of suicides associated with schizophrenia include prior suicide attempt, comorbid depression or higher depressive symptoms, early onset of illness, frequent psychiatric hospitalizations, and unemployment.[65,72–76] In the present study, most patients who completed suicide were documented as having multiple known risk factors for suicide, including younger age at onset of illness and a history of prior suicide attempts, which is a strong clinical correlate of an eventual successful suicide attempt.[75,77]

Overall, the crude incidence rate for completed suicide noted in this study (28.42 per 1,000 patient-years; 95% confidence interval [CI]: 7.74–72.76) was substantially higher than the pooled incidence data for PP1M from the 4 studies (NCT01685931, NCT01051531, NCT01515423, and current study) conducted in the People's Republic of China (7.06 per 1,000 patient-years; 95% CI: 2.29–16.47; Table 5) (unpublished data on file). Treatment with atypical antipsychotics has been favorably associated with reduction in suicidal intentions and a potential for protection against suicide via attenuation of symptom severity.[73,78] Further, based on cumulative experience from controlled Phase III studies of PP1M in Chinese patients with schizophrenia, the rates for completed suicide in the PP1M active treatment arms have been observed to be lower in comparison with placebo and risperidone LAI treatment arms. From case-level analysis, patients who completed suicides during the present study had a range of documented suicide-related risk factors. Thus, it is likely that the suicide rate in this study was related to patient selection.

The remaining 4 of the 8 deaths that occurred in the study were of unclear etiology. Two were classified as "unexplained", and 1 was classified as being "of cardiac origin" but this result was speculative since the autopsy failed to yield any other clear cause. Unfortunately, none of the 4 deaths were witnessed; all 4 patients were found dead (1 each in a "rental room", "by a river", "in bed", and "at home"). According to a previous study, mortality rates in schizophrenia were significantly greater than in the general population.[79] Cardiovascular disorders were the most common causes of sudden death in schizophrenia patients admitted to a psychiatric hospital, and sudden cardiac death occurred at a 0.8% rate in a psychiatric hospital, which is well above general population rates.[80] In the present study, 2 of 4 deaths of unclear etiology reported abnormal ECG at baseline suggestive of a possible cardiovascular involvement. Recent population-based studies from the People's Republic of China have presented age-stratified mortality rates among

Table 5 Death and suicide rates in clinical studies of paliperidone palmitate 1-month formulation conducted in the People's Republic of China

	Total number of patients	Number of events	Incidence rates (1,000 patient-years)	95% CI
Current study (NCT01947803)	353			
Deaths		8	56.83	24.54–111.98
Completed suicide		4	28.42	7.74–72.76
Other reasons		4	28.42	7.74–72.76
Unsuccessful suicide attempts		3	21.30	4.39–62.26
Multiple Chinese studies*	1,373			
Deaths		12	16.94	8.75–29.59
Completed suicide		5	7.06	2.29–16.47
Other reasons		7	9.88	3.97–20.36
Unsuccessful suicide attempts		6	8.47	3.11–18.44

Note: *A pooled analysis of the following studies: NCT01947803, NCT01685931, NCT01051531, and NCT01515423.

patients with schizophrenia[81] and noted higher mortality rates in younger patients that diminished greatly with increased age (standard mortality ratio, 18–29 years: 120.89; 70+ years: 4.95).[81,82] Similar to observations among patients who had fatal suicides in this study, the patients who died (all-cause) were young and had prolonged history of schizophrenia (≥5 years) as compared with patients who survived.

The crude incidence rates for deaths (all-cause) observed in this study were also considerably higher than the pooled data from 4 Chinese studies (including the current study) of PP1M (16.94 per 1,000 patient-years; 95% CI: 8.75–29.59; Table 5) and global studies (7.1 per 1,000 patient-years);[83] the pooled death rates from 3 studies excluding the present study range from 5.86 to 8.24 per 1,000 person-years (unpublished data on file). The all-cause mortality rates in the present study were also higher than that reported in a large observational (ZODIAC) study (13 per 1,000 patient-years) for other antipsychotics (ziprasidone and olanzapine).[84]

Based on the limited data from the 8 deaths reported during this study, the high crude incidence rate of completed suicides and deaths does not appear to indicate a definite association with PP1M treatment. The high suicide and all-cause mortality rates may be attributable to an interplay of preexisting pertinent risk factors,[72,81,82] limitations in analysis, and other study-related variables such as small sample size, low number of observed cases (completed suicides and suicide attempts), and wide CIs that limit the assessment of the validity of these findings. Furthermore, there is insufficient information to ascertain if there was a systematic bias involved in selection of high-risk patients. Thus, the findings from the current study do not represent a new identified risk for PP1M, and the benefit–risk assessment of PP1M remains positive and unchanged for the approved indications.

The higher occurrence of EPS-related events (27.2%) during this study was similar to that reported in earlier studies of PP1M in Chinese patients with schizophrenia.[25,26] Extrapyramidal disorder (15.3%) showed the highest incidence among the EPS-related events, although the EPS-rating scale (SAS; median score: 0.0) did not indicate any trend of Parkinsonism. Further, the higher incidences of EPS events did not appear to deter medication adherence or the patient's preferences for LAI in this study. The rates of other clinically significant TEAEs, including prolactin-related TEAEs and glucose-related TEAEs, were also generally comparable with previous studies of PP1M.[25,27,31,33,48]

The open-label design and absence of a comparator in the current study may have introduced an observational bias on the physicians, and the knowledge of treatment allocation may have resulted in reporting bias for subjective outcomes such as patient-reported end points.

To summarize, treatment with PP1M showed symptom improvement, and no new safety concerns were identified over a 6-month treatment period in a real-world setting. These results were comparable with available evidence, validating the long-term benefits of PP1M in Chinese patients with schizophrenia.

Acknowledgments

Author contributions

Drs Lili Zhang, Shangli Cai, Yu Feng, Weihong Liu, and Huafei Lu were responsible for the design, conduct, and data analysis of the study. Drs Jingping Zhao, Lehua Li, Jianguo Shi, Yi Li, Xiufeng Xu, and Keqing Li were the principal investigators of the study, contributed data, and participated in the development of the manuscript. Jianmin Zhuo was responsible for the statistical analyses and design/interpretation of study results. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All authors meet ICMJE criteria, and all those who fulfilled those criteria are listed as authors.

Disclosure

Drs Jingping Zhao, Lehua Li, Jianguo Shi, Yi Li, Xiufeng Xu, and Keqing Li were the principal investigators of this study and have received research support or fees as consultants from Xi'an Janssen Pharmaceutical Ltd., People's Republic of China. Drs Lili Zhang, Yu Feng, Jianmin Zhuo, Weihong Liu, and Huafei Lu are employees of Xi'an Janssen Pharmaceutical Ltd., People's Republic of China, which is a Johnson & Johnson company. Dr Shangli Cai was an employee of Xi'an Janssen Pharmaceutical Ltd., People's

Republic of China, at the time of study. The authors report no other conflicts of interest in this work.

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