CNS Spectrums

www.cambridge.org/cns

Comparing two transitioning strategies to paliperidone palmitate once-every-6-months

Christoph U. Correll[1,2,3,4], Karen L. Johnston[5], Ibrahim Turkoz[6], Michael Kutch[7], R. Karl Knight[6], Monica Doring[5] and Martha Sajatovic[8,9]

[1]Department of Psychiatry, Zucker Hillside Hospital, Glen Oaks, NY, USA; [2]Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA; [3]Department of Child and Adolescent Psychiatry, Charité – Universitätsmedizin Berlin, Berlin, Germany; [4]German Center for Mental Health (DZPG), Partner Site, Berlin, Germany; [5]Janssen Scientific Affairs, LLC, a Johnson & Johnson company, Titusville, NJ, USA; [6]Janssen Research & Development, LLC, Titusville, NJ, USA; [7]Cytel, Cambridge, MA, USA; [8]Neurological and Behavioral Outcomes Center, University Hospitals Cleveland Medical Center, Cleveland, OH, USA and [9]Department of Psychiatry, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Original Research

Cite this article: Correll CU, Johnston KL, Turkoz I, Kutch M, Knight RK, Doring M, and Sajatovic M (2024). Comparing two transitioning strategies to paliperidone palmitate once-every-6-months. *CNS Spectrums* **29**(6), 633–639.
https://doi.org/10.1017/S1092852924000476

Received: 08 March 2024
Accepted: 05 August 2024

Keywords:
Paliperidone palmitate; relapse-free; schizophrenia and psychotic disorders; long-acting injectable antipsychotic; adult psychiatry; mental health; clinical trials

Corresponding author:
Christoph U. Correll;
Email: CCorrell@northwell.edu

This article was originally published with an incorrect author list. A notice detailing this has been published, and the error rectified in the online PDF and HTML versions.

Abstract

Background. A double-blind, randomized, active-controlled, parallel-group, noninferiority trial (NCT03345342) demonstrated that paliperidone palmitate once-every-6-months (PP6M) was noninferior to paliperidone palmitate once-every-3-months (PP3M) in preventing relapse in clinically stable adults with schizophrenia. This post hoc analysis assessed efficacy and safety following transition to PP6M from paliperidone once-monthly (PP1M) versus PP3M.

Methods. Adults with schizophrenia who were clinically stable on moderate/high doses of PP1M or PP3M were randomly assigned 1:2 to dorsogluteal PP3M or PP6M treatment for 12 months. The primary efficacy measure was time to relapse during the 12-month DB phase. Secondary endpoints included change from DB baseline to endpoint in Positive and Negative Syndrome Scale (PANSS) total and subscale scores, Clinical Global Impression-Severity (CGI-S) scale score, and Personal and Social Performance (PSP) scale score. Safety was assessed by treatment-emergent adverse events (TEAEs), vital signs, and clinical laboratory tests.

Results. Of 702 patients in the study, 231 transitioned from PP1M to PP6M and 247 transitioned from PP3M to PP6M. Low relapse rates for PP6M were observed regardless of transition pathway (PP1M/PP6M: 7.8%; PP3M/PP6M: 7.3%). Changes from DB baseline to endpoint in PANSS total, PSP, and CGI-S scores were similar between transition groups. In the DB phase, ≥1 TEAE was observed in 61.0% and 63.2% of patients in the PP1M/PP6M and PP3M/PP6M, groups, respectively.

Conclusion. Adults with schizophrenia who transitioned to PP6M from either PP1M or PP3M experienced similarly low relapse rates. Additionally, symptom and functionality scores supported the primary analysis and, along with TEAE incidences, were comparable between transition groups.

Introduction

Schizophrenia is a serious, complex mental disorder that has a 1-year prevalence rate of approximately 1.2% in adults aged 18–54 years in the United States; onset typically occurs in late adolescence or early adulthood.[1-3] Long-acting injectable antipsychotics (LAIs) have been shown to have superior attributes to oral antipsychotics (OAPs) in the treatment of adult patients with schizophrenia owing to (1) reductions in hospitalizations and relapses[4-9]; (2) more consistent bioavailability, predictable pharmacokinetics and stable plasma medication levels[8,10]; (3) elimination of daily pill administration burden while allowing adherence transparency for healthcare professions[5,11]; and (4) greater rates of treatment persistence, with longer median time to discontinuation.[12-14] Furthermore, compared to no antipsychotic use, LAIs reduced all-cause mortality by 53% in patients with schizophrenia, with the greatest benefits observed with second-generation antipsychotic LAIs (61% reduction) and the smallest benefits observed with any OAP (36% reduction) or any first-generation antipsychotic (27% reduction).[15]

Paliperidone palmitate (PP) is a second-generation LAI that has been shown to be effective at maintaining symptom control and reducing risk of relapse and hospitalization for patients with schizophrenia.[16-22] Three formulations of PP are available: paliperidone palmitate once-monthly (PP1M),[23] paliperidone palmitate once-every-3-months (PP3M),[24] and paliperidone palmitate once-every-6-months (PP6M).[25] These different injection intervals provide clinicians and patients with a variety of options that can be tailored to patient needs and preferences. In some instances, PP1M may give more control to change the dosing of the PP injection, for example, in

patients who are still somewhat unstable or who are in the beginning of PP therapy where a longer injection interval may be less desirable. On the other hand, for stable patients, a continuous control of schizophrenia symptoms over a 3-monthly or 6-monthly injection interval may be preferable due to less need to return to the clinic for the injection, greater flexibility when traveling or when living far from the location where the PP injection is delivered.

PP6M was approved based on results from a 12-month, double-blind (DB), randomized, active-controlled, parallel-group, noninferiority study (NCT03345342) that demonstrated that PP6M was as effective as PP3M in delaying and preventing relapses in clinically stable adult patients with schizophrenia.[21] Relapse rates were 7.5% (36 of 478 patients) for PP6M and 4.9% (11 of 224 patients) for PP3M. PP6M is the first LAI with a considerably longer dosing interval than other currently available LAIs, providing continuous stability of schizophrenia symptoms for up to 6 months with one dose. Clinically stable patients with schizophrenia who wish to transition to PP6M may do so only if they have been adequately treated with PP1M for ≥4 months or PP3M for ≥1 injection cycle providing flexibility to both patient and clinician in clinical decision making.[25]

Here, we have assessed the efficacy and safety outcomes following the transition to PP6M from PP1M versus PP3M. We hypothesized that efficacy and safety outcomes would not differ but generalize across the two clinical strategies of transitioning to PP6M.

Methods

Study design and patients

This post hoc analysis assessed the efficacy and safety following transition to PP6M from PP1M versus PP3M in clinically stable adults with schizophrenia who participated in a 12-month, DB, randomized, active-controlled, parallel-group, noninferiority trial (NCT03345342) comparing PP6M with PP3M (Figure 1).[21] Eligible patients were men and women aged between 18 and 70 years who had a *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) diagnosis of schizophrenia for ≥6 months before screening and a Positive and Negative Syndrome Scale (PANSS) total score of <70 points at the time of screening. Patients were previously treated with PP1M, PP3M, injectable risperidone microspheres, or any OAP (except clozapine). Patients were excluded from the study if they met any of the following criteria: active primary *DSM-5* diagnosis other than schizophrenia; receiving any form of involuntary treatment (such as involuntary psychiatric hospitalization or court-mandated treatment); attempted suicide within 12 months prior to screening or at imminent risk of suicide or violent behavior, as clinically assessed by the investigator at the time of screening; *DSM-5* diagnosis of moderate or severe substance use disorder (excluding nicotine and caffeine) within 6 months of screening; history of neuroleptic malignant syndrome, tardive dyskinesia, or clinically significant and unstable medical illness; history of treatment-resistant schizophrenia (ie, failure to respond to two adequate trials of different antipsychotic medications with adequate doses); or intolerability or severe reactions to moderate or higher doses of antipsychotic medications.[21]

After screening and an open-label transition phase, clinically stable patients receiving moderate/high doses of PP1M (156/234 mg) or PP3M (546/819 mg) for one injection cycle in the open-label maintenance phase were randomly assigned 1:2 to PP3M (546/819 mg) or PP6M (1,092/1,560 mg) during the 12-month DB treatment phase. Patients randomly assigned to the PP3M (546/819 mg) during the DB treatment phase were used as a reference in this analysis. Patients received dorsogluteal injections of PP3M (four doses) or PP6M (two doses with alternating placebo injections to maintain blinding). The placebo injection was 20% Intralipid® (200 mg/mL) injectable emulsion and matched the appearance of the active treatment.[21] Due to differences in syringe sizes used for the administration of PP6M versus PP3M, the study drug administrator was unblinded and not allowed to perform any other study-related procedures or communicate patient-related information with study site personnel to ensure the integrity of the blind.[21]

This study was approved by independent ethics committees or institutional review boards.[21] The authors assert that this trial was

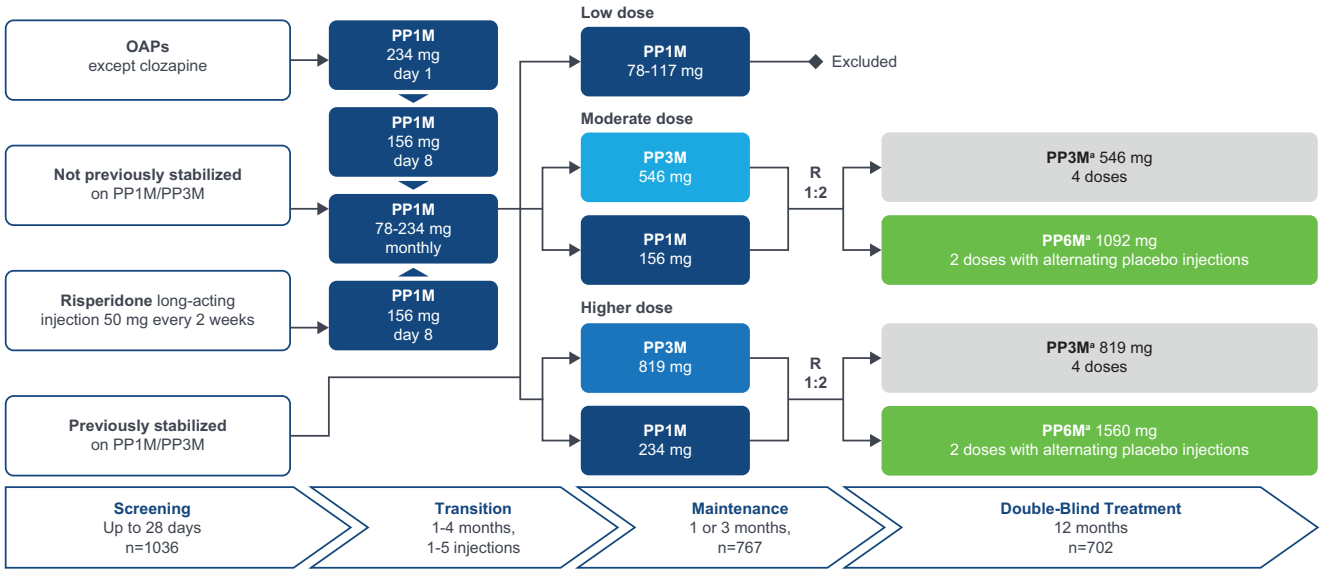

Figure 1. Study design. Abbreviations: OAP, oral antipsychotic; PP1M, paliperidone palmitate once-monthly; PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months; R, randomization. [a]PP3M and PP6M were administered dorsogluteally because of the larger volume of PP6M.

https://doi.org/10.1017/S1092852924000476 Published online by Cambridge University Press

conducted in compliance with the ethical principles of the Declaration of Helsinki of 1975 (revised 2008) and consistent with Good Clinical Practices and applicable regulatory requirements. All patients provided written informed consent.

Outcome measures

The primary outcome of this analysis measured differences in time to relapse for patients who transitioned to PP6M from PP1M (PP1M/PP6M) versus PP3M (PP3M/PP6M) during the DB phase. Summary statistics for those patients who were randomized to PP3M were also presented as a reference. Relapse criteria, defined as ≥1 of the following, were identical to those used in previous clinical studies of PP3M and PP1M[19,20]: (1) psychiatric hospitalization due to exacerbation of schizophrenia symptoms (involuntary or voluntary admission); (2) deliberate self-injury resulting in suicide or exhibited violent behavior resulting in clinically significant injury; (3) aggressive behavior, suicidal or homicidal ideation; (4) a 25% increase (for patients with PANSS scores of >40 at randomization) or 10-point increase (for patients with PANSS scores of ≤40 at randomization) in PANSS total score from randomization for two consecutive assessments between 3 and 7 days; or (5) PANSS items scores of ≥5 (if PANSS items was ≤3 at randomization) or ≥6 (if PANSS items was 4 at randomization) after randomization for two consecutive assessments between 3 and 7 days on any of the following items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness).[21]

Secondary efficacy endpoints included changes from baseline during the DB phase in PANSS total score and subscale scores, Clinical Global Impression-Severity (CGI-S) scale score, and Personal and Social Performance (PSP) scale score. Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, and clinical laboratory tests.

Statistical methods

The Kaplan–Meier method was used to estimate the 12-month cumulative estimate of rates of remaining relapse-free. Noninferiority between the different transitions through the PP profiles was concluded if the lower limit of the two-sided 95% CI of the difference in the relapse-free rates between the different transition groups exceeded −10% (the 10% noninferiority margin was selected based on the results of previous studies of PP1M and PP3M and on advice from a panel of experts in the field of schizophrenia, and health authorities and endorsed by the Committee for Medicinal Products for Human Use).[26,27] Moreover, a 10% difference in a categorical outcome translates into a number-needed-to-treat (NNT) of 10, and any NNT below 10 is generally seen as clinically relevant.[28] The change from baseline (DB) at each visit in PANSS total and subscale scores and CGI-S and PSP scores during the DB phase was analyzed using an analysis of the covariance model with factors for treatment and country and baseline score as a covariate.

Results

Patient characteristics

Of the 702 patients included in the DB phase, 231 transitioned from PP1M to PP6M and 247 transitioned from PP3M to PP6M.

Table 1. Baseline Demographics and Disease Characteristics

	PP1M/PP6M *n* = 231	PP3M/PP6M *n* = 247	PP3M *n* = 224	Total *N* = 702
Mean age (SD), years[a]	39.4 (11.91)	42.8 (11.42)	40.0 (10.98)	40.8 (11.53)
Male, *n* (%)	148 (64.1)	178 (72.1)	154 (68.8)	480 (68.4)
Race, *n* (%)				
White	174 (75.3)	179 (72.5)	168 (75.0)	521 (74.2)
Asian[b]	43 (18.6)	23 (9.3)	30 (13.4)	96 (13.7)
Black and/or African American	13 (5.6)	36 (14.6)	23 (10.3)	72 (10.3)
Ethnicity, *n* (%)				
Hispanic or Latino	38 (16.5)	37 (15.0)	25 (11.2)	100 (14.2)
Mean BMI (SD), kg/m^2	26.9 (4.79)	28.8 (4.96)	27.5 (4.96)	27.7 (4.96)
Mean age at first SCZ diagnosis (SD), years	28.0 (9.11)	27.4 (8.93)	27.5 (9.05)	27.6 (9.02)
Mean duration of illness (SD), years	11.4 (9.89)	15.5 (10.71)	12.5 (9.84)	13.2 (10.30)
Mean duration PH prior to study (SD), days[c]	63.3 (72.13)	62.8 (67.76)	44.6 (53.09)	57.2 (65.75)

Abbreviations: BMI, body mass index; PH, psychiatric hospitalization; PP1M, paliperidone palmitate once-monthly; PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months; SCZ, schizophrenia.
[a]Age at screening visit.
[b]Asian race subcategories include Chinese, Korean, Japanese, Filipino, Asian Indian, Thai, Malaysian, and other Asian races.
[c]Duration of the most recent hospitalization for psychosis any time prior to study start (not restricted to 24 months prior to study start).

Baseline demographic and disease characteristics were comparable between the PP1M/PP6M and PP3M/PP6M transition groups and the 224 patients within the PP3M arm (Table 1). The mean age for all patients was 40.8 years, 68.4% were male, 74.2% were White, and the baseline mean body mass index was 27.7 kg/m^2. The mean duration of illness at baseline was 13.2 years.

Efficacy

Relapse occurred in 7.8% of patients in the PP1M/PP6M group and 7.3% in the PP3M/PP6M group (Figure 2). The Kaplan–Meier estimate of the treatment group difference (95% CI) in the percentage of patients who remained relapse-free versus PP3M was −2.7% (−8.5 to 3.0) in the PP1M/PP6M group and −2.9% (−8.3 to 2.4) in the PP3M/PP6M group (Figure 3). The median time to relapse (the time at which the cumulative survival function equals 0.5 or 50%) was not estimable for any group because of the low number of relapses during the DB phase (Figure 2). The magnitudes of change from DB baseline to end point in PANSS total, PSP, and CGI-S scores were similar between groups (Table 2).

Safety

Of the 702 total patients, 428 (61.0%) had at least one TEAE during the DB phase, with TEAEs experienced by 61.0%, 63.2%, and 58.5% of patients in the PP1M/PP6M, PP3M/PP6M, and PP3M groups, respectively (Table 3). The most common TEAEs (occurring in

https://doi.org/10.1017/S1092852924000476 Published online by Cambridge University Press

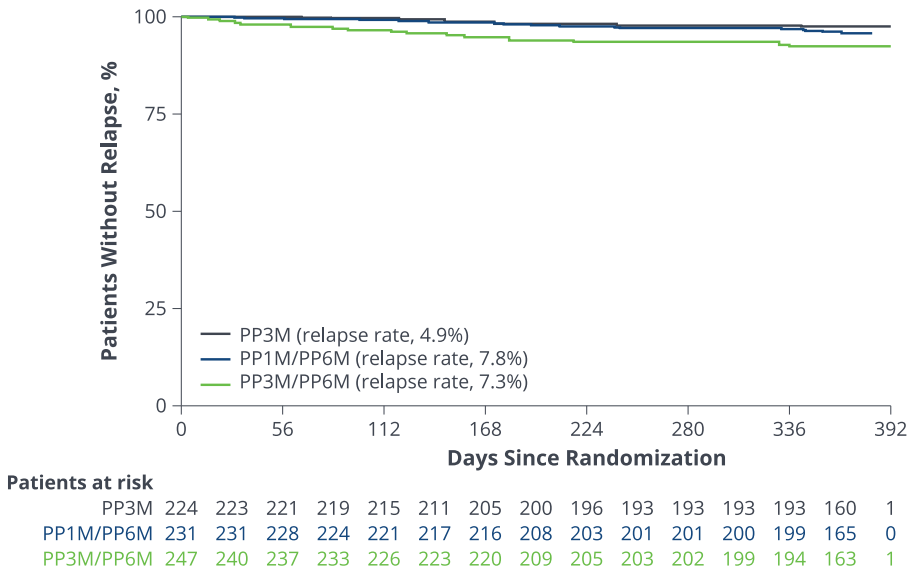

Figure 2. Kaplan–Meier plot of patients without relapse during the DB phase. Abbreviations: DB, double-blind; PP1M, paliperidone palmitate once-monthly; PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months.

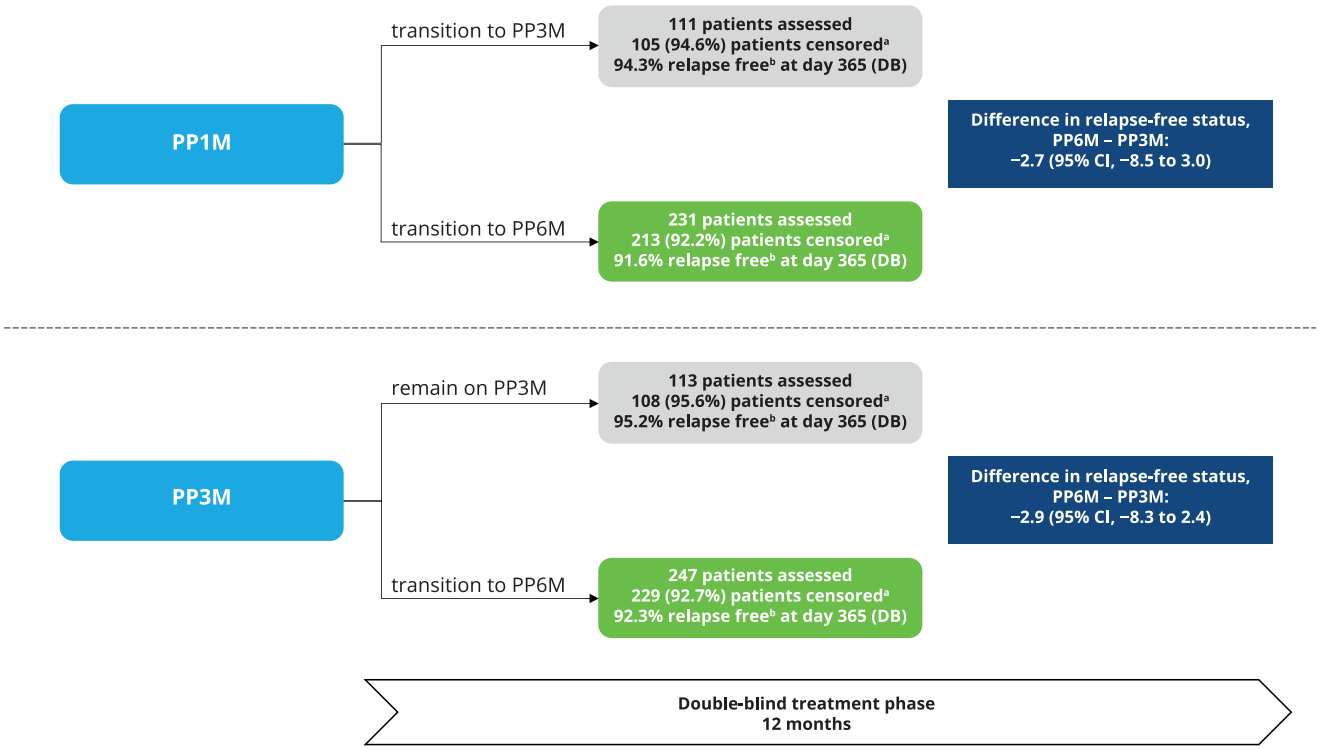

Figure 3. Number of patients who remained relapse free at the end of DB by maintenance dose (PP1M or PP3M). Abbreviations: DB, double-blind; PP1M, paliperidone palmitate once-monthly; PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months. [a]Censored data included patients who completed the DB phase without relapses and patients who withdrew early during the DB phase. [b]Based on Kaplan–Meier product limit estimates.

≥5% of patients) experienced in the PP1M/PP6M, PP3M/PP6M, and PP3M groups were weight increased, injection site pain, headache, nasopharyngitis, and upper respiratory infection (Table 3).

During the DB phase, the percentage of patients experiencing at least one serious TEAE was 5.2% (n = 12), 4.9% (n = 12), and 6.7% (n = 15) in the PP1M/PP6M, PP3M/PP6M, and PP3M groups, respectively. The most frequent serious TEAEs were related to psychiatric disorders (PP1M/PP6M: n = 8; PP3M/PP6M: n = 6; PP3M: n = 7), including schizophrenia (PP1M/PP6M: n = 4; PP3M/PP6M: n = 4; PP3M: n = 1). A total of 22 patients (3.1%) experienced a TEAE leading to drug withdrawal (PP1M/PP6M: n = 6; PP3M/PP6M: n = 10; PP3M: n = 6). Three deaths were reported during the DB phase (PP1M/PP6M: n = 1 [cause not specified]; PP3M: n = 2 [sudden death of unknown cause, and

https://doi.org/10.1017/S1092852924000476 Published online by Cambridge University Press

Table 2. Summary of Change From Baseline in PANSS, CGI-S, and PSP During the DB Phase

	PP1M/PP6M *n* = 231	PP3M/PP6M *n* = 247	PP3M *n* = 224
PANSS total score			
Mean at DB baseline (SD)	53.3 (9.52)	50.6 (9.51)	51.4 (9.77)
Mean change from baseline (SD)	−1.8 (9.74)	−1.8 (8.11)	−1.6 (7.40)
Mean PANSS subscale scores (SD)			
Positive subscale			
Baseline (DB)	11.3 (3.36)	10.7 (3.05)	10.8 (2.98)
Change from baseline	−0.1 (3.54)	−0.2 (3.06)	−0.1 (2.82)
Negative subscale			
Baseline (DB)	16.3 (4.06)	15.8 (4.32)	15.9 (4.18)
Change from baseline	−0.8 (2.85)	−0.6 (2.54)	−0.6 (2.61)
CGI-S score[a]			
Mean at DB baseline (SD)	3.0 (0.76)	3.0 (0.80)	3.0 (0.77)
Mean change from baseline (SD)	0.0 (0.77)	0.0 (0.63)	0.0 (0.63)
PSP score[b]			
Mean at DB baseline (SD)	66.5 (11.15)	66.2 (13.67)	66.5 (11.82)
Mean change from baseline (SD)	1.1 (7.31)	0.9 (6.94)	1.1 (8.11)

Abbreviations: CGI-S, Clinical Global Impression-Severity scale; DB, double-blind; PANSS, Positive and Negative Syndrome Scale; PP1M, paliperidone palmitate once-monthly; PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months; PSP, Personal and Social Performance scale.
[a]PP1M/PP6M, *n* = 228; PP3M/PP6M, *n* = 245; PP3M, *n* = 220.
[b]PP1M/PP6M, *n* = 229; PP3M/PP6M, *n* = 246; PP3M, *n* = 221.

Table 3. Overall Safety Summary (DB Phase)

	PP1M/PP6M *n* = 231	PP3M/PP6M *n* = 247	PP3M *n* = 224	Total *n* = 702
≥1 TEAE	141 (61.0)	156 (63.2)	131 (58.5)	428 (61.0)
≥1 possibly related TEAE	70 (30.3)	78 (31.6)	61 (27.2)	209 (29.8)
≥1 serious TEAEs	12 (5.2)	12 (4.9)	15 (6.7)	39 (5.6)
TEAEs leading to drug withdrawn	6 (2.6)	10 (4.0)	6 (2.7)	22 (3.1)
TEAEs leading to death	1 (0.4)	0 (0)	2 (0.9)	3 (0.4)
Most common (≥5%) TEAEs				
Weight increased	17 (7.4)	23 (9.3)	17 (7.6)	57 (8.1)
Injection site pain	11 (4.8)	26 (10.5)	9 (4.0)	46 (6.6)
Headache	19 (8.2)	13 (5.3)	12 (5.4)	44 (6.3)
Nasopharyngitis	10 (4.3)	12 (4.9)	13 (5.8)	35 (5.0)
Upper respiratory infection	7 (3.0)	17 (6.9)	9 (4.0)	33 (4.7)
Most common (≥1%) serious TEAEs				
Psychiatric disorders	8 (3.5)	6 (2.4)	7 (3.1)	21 (3.0)
Schizophrenia	4 (1.7)	4 (1.6)	1 (0.4)	9 (1.3)
Treatment-emergent abnormal plasma prolactin results by gender				
Female, *n*	83	68	69	220
High, *n* (%)[a]	11 (13.3)	13 (19.1)	14 (20.3)	38 (17.3)
Male, *n*	148	178	152	478
High, *n* (%)[a]	17 (11.5)	35 (19.7)	16 (10.5)	68 (14.2)

Abbreviations: DB, double-blind; PP1M, paliperidone palmitate once-monthly; PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months; TEAE, treatment-emergent adverse event.
Values are *n* (%) unless otherwise noted.
[a]High = baseline value ≤ normal range upper limit and postbaseline > normal range upper limit. For males, the reference range is 2.64–13.13 μg/L and for females the reference range is 2.74–26.72 μg/L.

pulmonary embolism, 1 each]), which investigators considered unrelated to the study medication. There were no deaths reported in the DB phase for PP3M/PP6M.

Discussion

This post hoc analysis found that adult patients with schizophrenia who transition to PP6M from either PP1M or PP3M experience similarly low relapse rates, with 91.6% of patients in the PP1M/PP6M group and 92.3% in the PP3M/PP6M remaining relapse-free up to 12 months. Assessments of schizophrenia symptoms, patient functioning, disease severity, and safety were similar between the transition groups, confirming that patients were clinically stable and well maintained on PP6M. Safety findings were consistent with the known profile of PP.[17-22] The type and incidence of TEAEs was comparable between the PP1M/PP6M, PP3M/PP6M, and PP3M groups, demonstrating a similar safety profile between the formulations. None of the most common TEAEs, including injection site pain and weight gain, were reported as serious. The sample patient population examined in this study is relatively representative of that seen in a clinical care setting in terms of sex, race, and baseline disease severity.

Treatment with LAIs has been shown to have superior efficacy to OAPs in reducing hospitalizations and relapses in patients with schizophrenia.[4-9] LAIs reduce the pill burden associated with the daily administration of OAPs and have been shown to lead to higher rates of treatment adherence and lower rates of relapse.[5] Additionally, LAIs provide the opportunity for healthcare practitioners to be aware of medication nonadherence by patients, and subsequent appropriate intervention can be taken to prevent further exacerbation of symptoms.[5] Transitioning clinically stable patients to an LAI with a longer dosing interval, such as PP6M, could provide more patient-focused care.[29,30] LAIs that have longer dosing intervals may be more advantageous to patients for a variety of reasons, including fewer injections required, a reduction in social stigma, and greater overall quality of life.[7,12,29] A comparative effectiveness analysis using a Medicare claims database showed that PP3M had a lower hazard ratio of discontinuation, treatment failure and relapse compared to twice-monthly risperidone LAI.[31] In addition, cost offsets from reduced administration and relapse costs due to adherence benefits suggest minimal budget impact to introducing PP6M as a treatment option.[32] The real-world performance of PP6M is currently being analyzed.

Ultimately, greater clinical stability through LAI use can facilitate uninterrupted psychosocial rehabilitation and counter self-stigma.[6,33,34] Together with extended injection intervals, which have been shown to decrease antipsychotic discontinuation risk,

https://doi.org/10.1017/S1092852924000476 Published online by Cambridge University Press

broader- and longer-injection-interval LAI use may facilitate greater reengagement with life and promote greater functional recovery than is currently achieved.[12,35,36]

Results of this study must be interpreted within its limitations. First, the subgroup sample sizes were small, which reduced the statistical power to identify potential group differences. However, the results of the PP1M/PP6M and PP3M/PP6M groups were very similar numerically, indicating that both clinical pathways to PP6M are valid clinical options. Second, the initial PP1M or PP3M treatment during the transition and maintenance phases prior to baseline of the DB phase was not randomized; however, all patients had to be clinically stable prior to the DB phase, and transitioning to PP3M or PP6M via PP1M is the approved initiation schedule,[7] increasing the generalizability of the results and supporting flexibility in the clinical initiation of PP6M. Third, the use of placebo injections for the PP6M groups limits interpretations related to the comparison of the dosing intervals between PP3M and PP6M and may introduce a potential placebo effect. Finally, despite the inability to estimate the median time to relapse, the low event rate of around 7% is clinically significant and suggests a positive effect of PP6M, in that the majority of patients did not experience a relapse. There is a risk that the current observation period may not be long enough to observe relapses in a significant proportion of patients which may introduce a bias in the event rate over a longer time period.

Conclusions

In conclusion, adults with schizophrenia who transitioned to PP6M from either PP1M or PP3M experienced similarly low rates of relapse with no new safety signals, providing clinicians and patients flexibility regarding treatment plans incorporating PP6M.

Acknowledgments. The authors thank Laura van Laeren, PhD (ApotheCom, Yardley, PA), for editorial and writing assistance, which was funded by Janssen Scientific Affairs, LLC, a Johnson & Johnson company. This manuscript is based on a poster presented at Psych Congress; September 6–10, 2023; Nashville, Tennessee.

Author contribution. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: M.K., I.T.

Data availability statement. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding. This study was supported by Janssen Scientific Affairs, LLC, a Johnson & Johnson company and the funder participated in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication.

Disclosure. C.U.C. has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Takeda, Teva, Tolmar, Vertex, and Viatris; provided expert testimony for Janssen and Otsuka; served on a Data Safety Monitoring Board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva; received grant support from Janssen Pharmaceuticals and Takeda; received royalties from UpToDate; and holds stock options in Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Mindpax, and Quantic. K.L.J. and M.D. are employees of Janssen Scientific Affairs, LLC, a Johnson & Johnson company. I.T. and K.K. are employees of Janssen Research & Development, LLC. K.L.J., I.T., and K.K. hold stock in Johnson & Johnson, Inc. M.K. is an employee of Cytel Inc. M.S. has received research grants from Merck, Otsuka, Alkermes, Intra-Cellular, Inc., International Society for Bipolar Disorders, National Institutes of Health, Centers for Disease Control and Prevention, and Patient-Centered Outcomes Research Institute; has served as a consultant for Alkermes, Janssen, Lundbeck, Neurelis, Otsuka, and Teva; and has received royalties from Johns Hopkins University Press, Oxford Press, Springer Press, and UpToDate; and has received compensation for preparation of and/or participating in continuing medical education activities for the American Academy of Child and Adolescent Psychiatry, American Epilepsy Society, American Physician's Institute (CMEtoGo), Clinical Care Options, Neurocrine, and Psychopharmacology Institute.

References

1. Simeone JC, Ward AJ, Rotella P, Collins J, Windisch R. An evaluation of variation in published estimates of schizophrenia prevalence from 1990—2013: a systematic literature review. *BMC Psychiatry.* 2015;**15**:193.
2. Charlson FJ, Ferrari AJ, Santomauro DF, et al. Global epidemiology and burden of schizophrenia: findings from the Global Burden of Disease study 2016. *Schizophr Bull.* 2018;**44**(6):1195–1203.
3. Narrow WE, Rae DS, Robins LN, Regier DA. Revised prevalence estimates of mental disorders in the United States: using a clinical significance criterion to reconcile 2 surveys' estimates. *Arch Gen Psychiatry.* 2002;**59**(2):115–123.
4. Wander C. Schizophrenia: opportunities to improve outcomes and reduce economic burden through managed care. *Am J Manag Care.* 2020;**26**(3 Suppl):S62–S68.
5. Brissos S, Veguilla MR, Taylor D, Balanzá-Martinez V. The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal. *Ther Adv Psychopharmacol.* 2014;**4**(5):198–219.
6. Correll CU, Citrome L, Haddad PM, et al. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. *J Clin Psychiatry.* 2016;**77**(suppl 3):1–24.
7. Højlund M, Correll CU. Switching to long-acting injectable antipsychotics: pharmacological considerations and practical approaches. *Expert Opin Pharmacother.* 2023;**24**(13):1463–1489.
8. McEvoy JP. Risks versus benefits of different types of long-acting injectable antipsychotics. *J Clin Psychiatry.* 2006;**67**(Suppl 5):15–18.
9. Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *The Lancet Psychiatry.* 2021;**8**(5):387–404.
10. Correll CU, Kim E, Sliwa JK, et al. Pharmacokinetic characteristics of long-acting injectable antipsychotics for schizophrenia: an overview. *CNS Drugs.* 2021;**35**(1):39–59.
11. Haddad PM, Correll CU. Long-acting antipsychotics in the treatment of schizophrenia: opportunities and challenges. *Expert Opin Pharmacother.* 2023;**24**(4):473–493.
12. Takács P, Kunovszki P, Timtschenko V, et al. Comparative effectiveness of second generation long-acting injectable antipsychotics based on nationwide database research in Hungary: an update. *Schizophrenia Bulletin Open.* 2022;**3**(1):sgac013.

https://doi.org/10.1017/S1092852924000476 Published online by Cambridge University Press

13. Rubio JM, Taipale H, Tanskanen A, Correll CU, Kane JM, Tiihonen J. Long-term continuity of antipsychotic treatment for schizophrenia: a nationwide study. *Schizophr Bull.* 2021;**47**(6):1611–1620.
14. Pai N, McGeachie AB, Puig A, Huang TH, Brahmbhatt P. Persistence and adherence to second-generation antipsychotic long-acting injectable medications for schizophrenia: a comparative study in the Australian context. *Australas Psychiatry.* 2023;**31**(1):76–81.
15. Correll CU, Solmi M, Croatto G, et al. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. *World Psychiatry.* 2022;**21**(2):248–271.
16. Mathews M, Gopal S, Nuamah I, et al. Clinical relevance of paliperidone palmitate 3-monthly in treating schizophrenia. *Neuropsychiatr Dis Treat.* 2019;**15**:1365–1379.
17. Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M, Hough D. A 52-week open-label study of the safety and tolerability of paliperidone palmitate in patients with schizophrenia. *J Psychopharmacol.* 2011;**25**(5):685–697.
18. Hough D, Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *Schizophr Res.* 2010;**116**(2–3):107–117.
19. Berwaerts J, Liu Y, Gopal S, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial. *JAMA Psychiatry.* 2015;**72**(8):830–839.
20. Savitz AJ, Xu H, Gopal S, et al. Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, noninferiority study. *Int J Neuropsychopharmacol.* 2016;**19**(7):pyw018.
21. Najarian D, Sanga P, Wang S, et al. A randomized, double-blind, multicenter, noninferiority study comparing paliperidone palmitate 6-month versus the 3-month long-acting injectable in patients with schizophrenia. *Int J Neuropsychopharmacol.* 2022;**25**(3):238–251.
22. Najarian D, Turkoz I, Knight RK, et al. Long-term efficacy and safety of paliperidone 6-month formulation: an open-label 2-year extension of a 1-year double-blind study in adult participants with schizophrenia. *Int J Neuropsychopharmacol.* 2023;**26**(8):537–544.
23. Janssen Pharmaceuticals Inc. INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use [highlights of prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2022.
24. Janssen Pharmaceuticals Inc. INVEGA TRINZA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use [highlights of prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2021.
25. Janssen Pharmaceuticals Inc. INVEGA HAFYERA™ (paliperidone palmitate) extended-release injectable suspension, for gluteal intramuscular use [highlights of prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2021.
26. US Food & Drug Administration. Non-inferiority clinical trials to establish effectiveness: guidance for industry. US Food & Drug Administration. 2018. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm202140.pdf. Accessed July 2, 2024.
27. Committee for Medicinal Products for Human Use (CHMP). Guidelines on the choice of the non-inferiority margin. 2006. www.ema.europa.eu/en/documents/scientific-guideline/guideline-choice-non-inferiority-margin_en.pdf. Accessed July 2, 2024.
28. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Int J Clin Pract.* 2013;**67**(5):407–411.
29. Pietrini F, Albert U, Ballerini A, et al. The modern perspective for long-acting injectables antipsychotics in the patient-centered care of schizophrenia. *Neuropsychiatr Dis Treat.* 2019;**15**:1045–1060.
30. Blackwood C, Sanga P, Nuamah I, et al. Patients' preference for long-acting injectable versus oral antipsychotics in schizophrenia: results from the patient-reported medication preference questionnaire. *Patient Prefer Adherence.* 2020;**14**:1093–1102.
31. Li P, Geng Z, Benson C, Patel C, Joshi JA. Real-world comparative effectiveness of antipsychotic agents in a national sample of Medicare beneficiaries with schizophrenia in the United States. Poster presented at: the American Psychiatric Association Annual Meeting; May 4–8, 2024; New York, NY.
32. Phelps H, Lin D, Keenan A, et al. Budget impact of introducing once-every-6-months paliperidone palmitate in US health care plans. *J Manag Care Spec Pharm.* 2023;**29**(3):303–313.
33. Fond G, Vidal M, Joseph M, et al. Self-stigma in schizophrenia: a systematic review and meta-analysis of 37 studies from 25 high- and low-to-middle income countries. *Mol Psychiatry.* 2023;**28**(5):1920–1931.
34. Gerlinger G, Hauser M, De Hert M, Lacluyse K, Wampers M, Correll CU. Personal stigma in schizophrenia spectrum disorders: a systematic review of prevalence rates, correlates, impact and interventions. *World Psychiatry.* 2013;**12**(2):155–164.
35. Arango C, Fagiolini A, Gorwood P, et al. Delphi panel to obtain clinical consensus about using long-acting injectable antipsychotics to treat first-episode and early-phase schizophrenia: treatment goals and approaches to functional recovery. *BMC Psychiatry.* 2023;**23**(1):453.
36. Correll CU, Ismail Z, McIntyre RS, Rafeyan R, Thase ME. Patient functioning and life engagement: unmet needs in major depressive disorder and schizophrenia. *J Clin Psychiatry.* 2022;**83**(4):LU21112AH1.