Comparative analysis of relapse rates with paliperidone palmitate 6-month in patients with schizophrenia: randomized controlled trial vs matched real-world data

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Introduction

- Poor adherence to oral antipsychotics (OAs) is an established risk factor for relapses in schizophrenia, and long-acting injectable (LAI) formulations improve adherence and support symptomatic and functional remission by ensuring steady exposure with less frequent dosing.[1,2]
- Paliperidone palmitate (PP) is a unique LAI that offers multiple dosing intervals: monthly (PP1M), 3-monthly (PP3M), and most recently, 6-monthly (PP6M).[3,4]
- In the phase 3 randomized clinical trial (RCT) (NCT03345342), PP6M demonstrated noninferiority to PP3M in relapse prevention and in symptomatic and functional outcomes, with benefits sustained over a 2-year extension
- PP6M is approved for adults with schizophrenia adequately stabilized on PP1M or PP3M, and applicability to broader real-world (RW) populations is not known.[5,6]

Objective

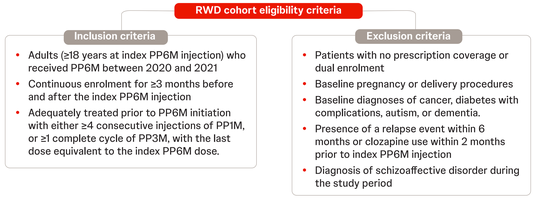
To compare the 12-month relapse rates from the phase 3 RCT population (n=478) with the relapse rate obtained from a comparable RW adult schizophrenia cohort transitioning to PP6M, to assess the generalizability of clinical data for PP6M to broader RW settings.

Methods

Study Design

- In this comparative analysis, real-world data (RWD) were obtained from the Merative™ MarketScan® Multi-State Medicaid Database (MDCD), a large, nationally representative claims database in the United States that captures patient-level information on enrolment, demographics, diagnoses, procedures, and prescription drug use.
- Adult patients who had ≥3 months of continuous enrollment before and after their first (index) PP6M injection were included in the RWD cohort (**Figure 1**). This RWD cohort was matched to the RCT participants based on RCT inclusion and exclusion conditions.

FIGURE 1: Study Design



Analysis

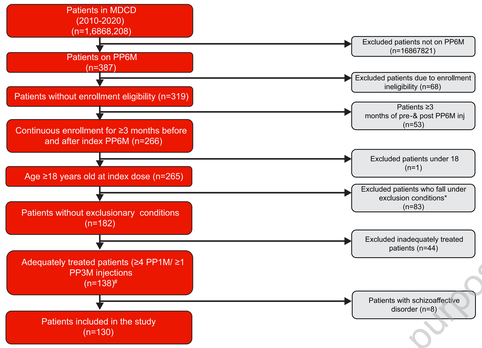
- Risk differences in relapse rates between PP6M-RCT and PP6M-RWD studies were examined using causal inference methods (propensity score (PS) matching, propensity score treatment weighting (IPTW), doubly robust methods (augmented inverse probability weighting [AIPW]; target maximum likelihood estimation [TMLE]), and Kaplan-Meier curves.
- The primary endpoint was the 12-month relapse rate after the index PP6M injection.
- Relapse was defined as ≥1 episodes of psychiatric hospitalization due to schizophrenia symptoms, participant behavior resulting in harm (self-injury, suicide, harm to another person, or property damage), or suicidal or homicidal ideation.
- The PS matching model included age at index, gender, and index dose strength. Balance between cohorts was assessed using standardized mean differences (SMD).
- Time-to-relapse was also analyzed using Kaplan-Meier estimates.

Results

Patients

- A total of 129 out of 130 adult patients were included in the final RWD following the 1:1 PS matching to patients from the RCT (**Figure 2**). One patient was excluded from the final analysis due to lack of propensity score common support since its calculated propensity score did not overlap with the scores of the RCT.

FIGURE 2. RWD cohort selection



*Including cancer, diabetes with complications, autism, dementia, relapse event within 6 months prior to index PP6M injection, #with last dose equivalent to index PP6M dose. MDCD, Merative™ MarketScan® Multi-State Medicaid Database; PP1M, paliperidone palmitate 1-month formulation; PP3M, paliperidone palmitate 3-month formulation; PP6M, paliperidone palmitate 6-month formulation.

- The mean (SD) ages for clinical study and RWD cohorts were 37.5 (11.2) and 37.6 (11.3) years, respectively (SMD: <0.10).
- Both the clinical study and RWD cohorts included more men (69%), and 64.3% of patients in both cohorts received the high index PP6M dose (1000 mg eq. paliperidone).

TABLE 1: Patient characteristics

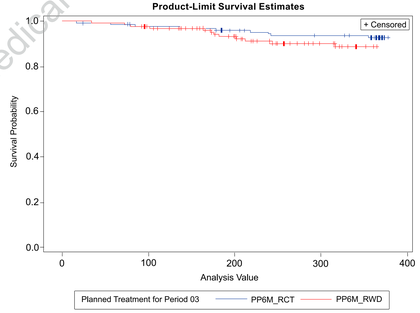
Characteristic	Clinical study cohort (n=129)	RWD cohort (n=129)
Age at index, years, mean (SD)	37.5 (11.17)	37.6 (11.30)
Sex, n (%)		
Women	40 (31.0%)	30 (31.0%)
Men	89 (69.0%)	89 (69.0%)
Index PP6M dose, n (%)		
Moderate	46 (35.7%)	46 (35.7%)
High	83 (64.3%)	83 (64.3%)
Post-index enrollment, days, mean (SD)	-	291.1 (87.60)
CCI score, mean (SD)	-	0.4 (0.70)
Elixhauser Comorbidity Index Score, mean (SD)		2.7 (1.91)

AIPW, augmented inverse probability weighting; IPTW, inverse probability of treatment weighting; RCT, randomized controlled trial; RWD, real-world data; PP6M, paliperidone palmitate 6-month formulation; TMLE, targeted maximum likelihood estimation.

Relapse rate

- The 12-month relapse rate was 7.0% in the clinical study cohort and 9.3% in the RWD cohort, corresponding to a risk difference of −2.3% (95% CI: −9.0%; 4.3%).
- Kaplan–Meier analysis demonstrated no significant difference in the median time-to-relapse (median was not reached) between cohorts (log-rank p=0.3110; **Figure 3**).
- Additional analyses using 1:2 PS matching, IPTW, and doubly robust methods (AIPW, TMLE) yielded consistent results.

FIGURE 3. Kaplan-Meier curve of median time to relapse in the clinical study and RWD cohorts



RCT, randomized controlled trial; RWD, real-world data; PP6M, paliperidone palmitate 6-month formulation

- Percent relpase risk differences ranged from -0.57% to -1.55%; in all cases, the 95% CIs included no difference of 0%.

TABLE 2: Relapse risk difference between RCT and RWD assessed using different methods

	PP6M-RCT	PP6M-RWD	Risk difference (95% CI)
1-1 matching	7.0% (9/129)	9.3% (12/129)	-2.33% (-8.99%; 4.34%)
1-2 matching	8.3% (21/253)	9.3% (12/129)	1.00% (-7.06%; 5.05%)
IPTW naïve	7.8% (36/478)	9.2% (12/130)	-1.40% (-7.03%; 4.22%)
IPTW trimmed	8.0% (36/454)	9.2% (12/130)	-1.22% (-6.87%; 4.43%)
IPTW trimmed normalized	8.0% (36/454)	9.2% (12/130)	-1.22% (-6.87%; 4.43%)
AIPW	8.2% (36/454)	9.1% (12/130)	-0.87% (-6.38%; 4.64%)
TMLE	7.6% (36/478)	8.9% (12/130)	-1.13% (-6.71%; 4.45%)

AIPW, augmented inverse probability weighting; IPTW, inverse probability of treatment weighting; RCT, randomized controlled trial; RWD, real-world data; PP6M, paliperidone palmitate 6-month formulation; TMLE, targeted maximum likelihood estimation.

Conclusions

- This comparative analysis supports the generalizability of PP6M effectiveness from a controlled RCT setting to RW practice among adequately treated adult patients with schizophrenia.
- The 12-month relapse rate in the RW population was low and consistent with the findings from the RCT.
- PP6M, with a dosing frequency of every 6 months, is a treatment option for adequately stabilized adults with schizophrenia, with the potential of low risk of relapse including in real-world setting.

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Disclosures

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