Earlier Use of Long-Acting Injectable Paliperidone Palmitate versus Oral Antipsychotics in Patients With Schizophrenia: A Post-hoc Analysis From PROSIPAL

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Background

- According to the critical period concept (rapid progression of illness within the first 3-5-years), treatment within the first five years of a schizophrenia diagnosis is considered optimal as early intervention leads to better outcomes.[1,2]
- Prior analyses have shown the benefits of implementing paliperidone palmitate 1-month (PP1M) versus oral antipsychotics (OAPs) within the critical period.[3]
- Given the rapid disease progression during this period, examining the impact of early LAI intervention on clinical outcomes could help inform clinicians of the benefits in treating patients earlier.[4]
- The objective of this analysis is to evaluate clinical outcomes following initiation of PP1M vs OAPs within ≤3-years and >3-5-years of a schizophrenia diagnosis.

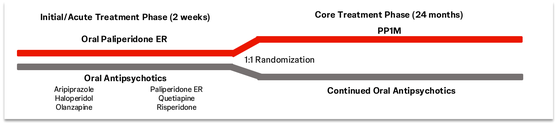
Methods

- This was a post hoc analysis of the PROSIPAL trial (NCT01081769), a 24-month, international, prospective, randomized, open-label, rater-blinded, multicenter, study in recently diagnosed (within 1-5 years) adults with schizophrenia (**Figure 1**).
  - The study consisted of a 2-week initial acute oral treatment phase followed by a 24-month treatment phase with PP1M or continued OAP
- Efficacy and safety outcomes were evaluated in patients receiving PP1M or OAP by varying durations of illness from schizophrenia diagnosis: ≤ 3 years and >3-5 years

Assessments

- Risk of relapse was evaluated within each subgroup. Hazard ratios (HRs) and 95% confidence intervals (CIs) for between-group differences in the risk of relapse were determined based on a Cox proportional hazards model.
- Changes in the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), and Personal and Social Performance (PSP) scale were assessed for both subgroups. Treatment group differences were evaluated using either t-test or Wilcoxon two-sample test.
- Additional outcomes were evaluated between the treatment groups within each subgroup including improvements in the Patient Treatment Satisfaction (TSQM) scale (effectiveness, side effects, convenience, and global satisfaction) and the Physician Treatment Satisfaction scale (efficacy, safety, mode of administration, and overall satisfaction).
- Treatment-emergent adverse events (TEAEs) were documented

FIGURE 1: PROSIPAL Study Design[5]



*Time to relapse was defined as any of the following: psychiatric hospitalization, an increase in the level of psychiatric care and an increase of 25% from baseline in the PANSS total score (or an increase of 10 points if baseline score ≤40), deliberate self-injury, suicidal or homicidal ideation, violent behavior resulting in injury to another person or property damage, substantial clinical deterioration, or required dose of antipsychotic exceeds the maximum approved dose

Results

Patient Baseline Characteristics

- A total of 715 patients were included in the intention-to-treat analysis set.
- Patient demographics and baseline characteristics are summarized in **Table 1**.

Table 1. Baseline Characteristics

Characteristic, Mean (SD)	≤3 Years		>3-5 Years	
	PP1M n=228	OAP n=246	PP1M n=124	OAP n=117
Age at screening visit, years,	32.1 (10.4)	32.3 (10.1)	33.6 (11.2)	33.3(10.0)
Sex, n (%)				
Men	137 (60.1)	135 (54.9)	76 (61.3)	66 (56.4)
Age at first diagnosis of schizophrenia, years	30.3 (10.4)	30.6 (10.1)	29.6 (11.1)	29.2(10.2)
Years from diagnosis of schizophrenia to the start of the study, years	2.1 (0.8)	2.1 (0.8)	4.5 (1.8)	4.5 (1.4)
Number of previous hospitalizations,	2.7 (1.7)	2.8 (1.8)	3.8 (2.6)	3.9 (2.7)
PANSS score	82.6 (12.7)	81.3 (11.6)	82.2 (10.8)	81.8 (11.9)
PSP score	54.6 (11.7)	55.9 (11.6)	56.4 (10.6)	54.0 (9.7)
CGI-S score	3.9 (0.4)	3.8 (0.4)	3.8 (0.4)	3.9 (0.3)

CGI-S, Clinical Global Impression-Severity Scale; PANSS, Positive and Negative Syndrome Scale; PP1M, paliperidone palmitate 1-month formulation; PSP, Personal and Social Performance scale; SD, standard deviation.

Safety

- Treatment-emergent adverse events (TEAE) rates were similar between treatment groups regardless of duration of illness.

Table 2. TEAEs in ≥10% of Patients

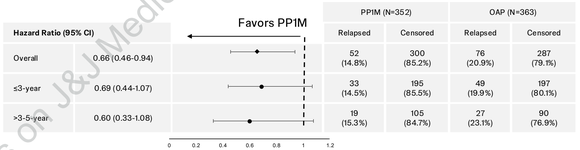
N (%)	≤3 Years N=474		>3-5 Years N=241	
	PP1M n=228	OAP n=246	PP1M n=124	OAP n=117
Patients with TEAE	170 (74.6)	156 (63.4)	81 (65.3)	69 (59.0)
TEAEs Occurring in ≥10% of Patients				
Weight Increased	43 (18.9)	43 (17.5)	13 (10.5)	20 (17.1)
Headache	26 (11.4)	18 (7.3)	13 (10.5)	13 (11.1)
Schizophrenia	21 (9.2)	27 (11.0)	8 (6.5)	8 (6.8)
Insomnia	21 (9.2)	23 (9.4)	13 (10.5)	6 (5.1)

OAP, oral antipsychotic; PP1M, paliperidone palmitate 1-month formulation; TEAE, treatment-emergent adverse event

Risk of Relapse

- The overall risk of relapse was reduced by 34% with PP1M versus OAP in the overall study population (HR 0.66; 95% CI 0.46-0.94).
- The risk of relapse was reduced by 31% with PP1M versus OAP (HR 0.69; 95% CI 0.44-1.07) in ≤3-years group and by 40% with PP1M vs OAP (HR 0.60; 95% CI 0.33-1.08) in >3-5 years group.
- Fewer relapses were observed with PP1M versus OAP in the ≤3-years group (14.5% and 19.9%, respectively) and the >3-5-year group (15.3% and 23.1%, respectively).

Figure 2. Forest Plot of Hazard Ratios (HR) of Time to Relapse by Treatment Group (PP1M vs OAP [95% CI]) by Duration of Illness Group; ITT Analysis Set Subjects



Hazard Ratio (95% CI)		PP1M (N=352) Relapsed	PP1M (N=352) Censored	OAP (N=363) Relapsed	OAP (N=363) Censored
Overall	0.66 (0.46-0.94)	52 (14.8%)	300 (85.2%)	76 (20.9%)	287 (79.1%)
≤3-year	0.69 (0.44-1.07)	33 (14.5%)	195 (85.5%)	49 (19.9%)	197 (80.1%)
>3-5-year	0.60 (0.33-1.08)	19 (15.3%)	105 (84.7%)	27 (23.1%)	90 (76.9%)

Regression analysis of survival data based on a Cox proportional hazards model with factor of years from diagnosis of schizophrenia to start of the study (0-3 vs >3 years), treatment (PP1M vs Oral), and prior years of schizophrenia treatment (P=0.72).

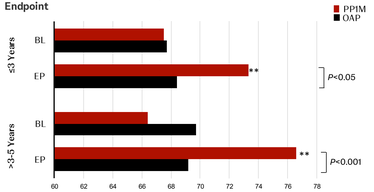
Change in PANSS, PSP, and CGI-S

- For the ≤3-years group, improvements were observed with PP1M vs OAP at the endpoint in PANSS total score (mean change -16.8 vs -13.2, p=0.044). Improvements were also seen with PP1M vs OAP at endpoint in PSP total score (mean change of 10.5 vs 7.7, p=0.031). No significant differences were observed between subgroups in CGI-S scores.
- For the >3-5-year group, no significant differences were observed between groups for PANSS, PSP, and CGI-S scores.

Change in TSQM and Physician Treatment Satisfaction

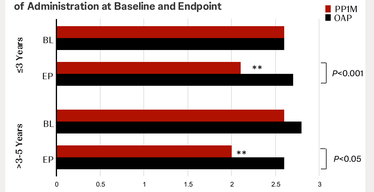
- For the ≤3-year group, improvements were observed with PP1M vs OAP at endpoint in TSQM convenience subscale (5.8 vs 0.7, p=0.025) and Physician Treatment Satisfaction mode of administration subscale (mean change -0.5 vs 0.1, p<0.001) (**Figure 3 & 4**). A mean change of -0.2 vs 0.1 (p=0.014) was observed in overall satisfaction with PP1M vs OAP, respectively.
- For the >3-5-year group, improvements were observed with PP1M vs OAP at the endpoint in TSQM-convenience (mean change 10.3 vs -0.5, p<0.001) and Physician Treatment Satisfaction mode of administration (mean change -0.6 vs -0.2, p=0.004). (**Figure 3 & 4**).

Figure 3. Mean Subscore in TSQM Convenience Subscale at Baseline and Endpoint



*P<0.05; **P < 0.001; P values for within-group comparisons are based on a Wilcoxon signed rank test. P values for between-group comparisons were based on Wilcoxon two-sample test.
BL, baseline; EP, endpoint; OAP, oral antipsychotic; PP1M, paliperidone palmitate 1-month.

Figure 4. Mean Score in Physician Treatment Satisfaction for Mode of Administration at Baseline and Endpoint



*P<0.05; **P<0.001; P values for within-group comparisons are based on a Wilcoxon signed rank test. P values for between-group comparisons were based on Wilcoxon two-sample test.
BL, baseline; EP, endpoint; OAP, oral antipsychotic; PP1M, paliperidone palmitate 1-month.

Conclusions

- This analysis showed that PP1M provides improvements in outcomes consistently within the first 3 years and >3-5 years of treatment compared to OAPs.
- The findings reinforce the importance of early adoption and implementation of PP1M post-schizophrenia diagnosis.
- Treatment-emergent adverse events rates were similar between treatment groups regardless of duration of illness.

Limitations

- Patients may not be fully representative of the real-world population with recent onset schizophrenia due to patients being enrolled in clinical trials with specific inclusion/exclusion criteria
- Given the limited sample size of the subgroups, the reliability of p-values may be compromised due to variability and potential imprecision.
- The original study was not designed to examine differences within duration of illness subgroups

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MD, LL, CO, KJ, JS, and TC are employees of Janssen Scientific Affairs, a Johnson & Johnson Company. IT is an employee of Janssen Research & Development, a Johnson & Johnson Company. MD, LL, CO, KJ, JS, and TC hold stock in Johnson & Johnson, Inc.

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