Earlier Use of Long-Acting Injectable Paliperidone Palmitate versus Oral Antipsychotics in Patients With Schizophrenia: An Integrated Patient-Level Post Hoc Analysis of the PRIDE and PROSIPAL studies

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Introduction

- Early intervention in schizophrenia is critical because with each subsequent relapse, there is further functional deterioration, decreased response to treatment, and worsening of clinical outcomes[1]
- Relapses in schizophrenia may decrease or delay the effectiveness of subsequent treatments[2]
- Therapeutic interventions during the critical period, the first 3–5 years following schizophrenia diagnosis, can positively impact schizophrenia outcomes[1,3]
- A prior integrated patient-level analysis revealed that implementing paliperidone palmitate (PP) earlier in the course of schizophrenia provides significant benefit compared to oral antipsychotics (OAPs)[4]
- Given the benefits of PP over OAPs in patients recently diagnosed with schizophrenia, it is of clinical interest to examine the advantages of PP by varying durations of illness

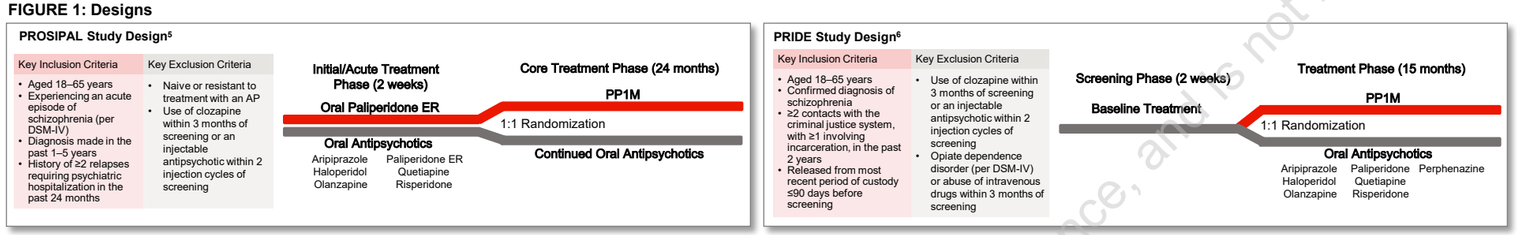
Objective

- This patient-level post hoc analysis evaluated the risk of relapse in adults with schizophrenia overall and by varying durations of illness (0–3-years, >3–5-years, and >5-years) receiving PP or OAP treatment

Methods

- Patients from the Janssen-sponsored PRIDE (NCT01157351) & PROSIPAL (NCT01081769) studies were included in the post hoc analysis (**Figure 1**)
- These studies were chosen because they had similar inclusion and exclusion criteria and definitions for relapse or treatment failure (TF). Authors had access to patient-level data.
- TF (relapse) was defined differently across studies but included relapses due to psychiatric hospitalizations, arrest or incarceration, suicidal or homicidal ideation or behavior, discontinuation due to inadequate efficacy and/or safety or tolerability, treatment supplementation due to inadequate efficacy, and worsening of symptoms (based on the Positive and Negative Syndrome Scale or the Clinical Global Impressions Scale)
- Cumulative distribution functions of time to TF or relapse were estimated using the Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) for between-group differences in risk of TF or relapse were based on a Cox proportional hazards model
- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were documented

FIGURE 1: Designs



Results

- A total of 1157 patients were included in the patient-level intention-to-treat analysis set (0–3 years: PP, n=253, OAP, n=263; >3–5 years: PP, n=138, OAP, n=134; >5 years: PP, n=187, OAP, n=182); most patients were male (68.7%), with a mean age of 34.7 years
- Patient disposition, demographic/baseline characteristics, and discontinuation rates are summarized in **Table 1**

TABLE 1: Baseline Characteristics

	0–3 Years N=516		>3–5 Years N=272		>5 Years N=369	
	PP	OAP	PP	OAP	PP	OAP
Number of Subjects	253	263	138	134	187	182
Mean age, years (SD)	31.9 (10.4)	32.3 (10.0)	33.1 (10.9)	33.4 (10.3)	39.3 (10.1)	39.7 (9.9)
Male, n (%)	161 (63.6%)	152 (57.8%)	87 (63.0%)	81 (60.4%)	158 (84.5%)	156 (85.7%)
Age of 1st Psychiatric Diagnosis, years N (SD)	253	263	138	134	187	182
Mean (SD)	30.1 (10.4)	30.5 (10.1)	29.2 (11.0)	29.3 (10.4)	20.9 (9.1)	20.7 (8.9)
Age of 1st Psychiatric Treatment, years N (SD)	253	262	138	134	187	182
Mean (SD)	29.1 (10.2)	29.5 (10.0)	28.5 (11.0)	28.7 (10.3)	22.1 (9.4)	22.2 (9.5)
Age of 1st Psychiatric Hospitalization, years, N (SD)	238	241	130	125	186	182
Mean (SD)	28.5 (11.5)	29.0 (10.0)	27.9 (11.5)	27.7 (11.4)	18.4 (11.6)	19.1 (12.2)
Total Psychiatric Hospitalization, N (SD)	232	238	126	120	147	144
Mean (SD)	2.6 (1.7)	2.9 (2.2)	3.9 (3.0)	4.1 (3.4)	8.1 (17.8)	5.8 (5.5)
Subjects Discontinued Study, N	64 (25.3%)	80 (30.4%)	33 (23.9%)	35 (26.1%)	116 (62.0%)	111 (61.0%)

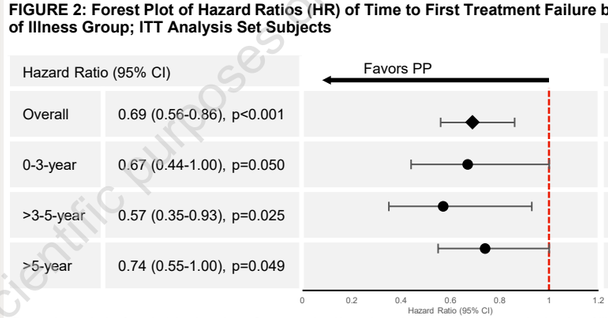
Efficacy

- The risk of relapse was reduced by 31% for patients receiving PP versus OAP (HR 0.69; 95% CI 0.56-0.86, p<0.001), independent of duration of illness category (**Figure 2**)
  - Overall, fewer relapses were observed with PP versus OAP (25.2% and 32.9%, respectively) (**Figure 3**)
- Risk of relapse was reduced by 33% for patients receiving PP versus OAP in the 0–3-year group (HR 0.67; 95% CI 0.44-1.00, p=0.050), by 43% in the >3–5-year group (HR 0.57; 95% CI 0.35-0.93, p=0.025) and by 26% in the >5-year group (HR 0.74; 95% CI 0.55-1.00, p=0.049) (**Figure 2**)

Safety

- A total of 875 (75.6%) patients experienced a treatment-emergent adverse event (TEAE) (0–3 years: PP, n=197 [77.9%], OAP, n=182 [69.2%]; >3–5 years: PP, n=99 [71.7%], OAP, n=93 [69.4%]; >5 years: PP, n=155 [82.9%], OAP, n=149 [81.9%]) (**Table 2**)
  - The most common TEAEs (TEAEs occurring ≥10% of patients) included injection site pain, nasopharyngitis, weight increase, akathisia, headache, anxiety, insomnia, & schizophrenia (**Table 2**)

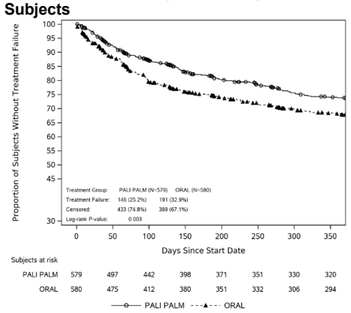
FIGURE 2: Forest Plot of Hazard Ratios (HR) of Time to First Treatment Failure by Treatment Group (PP vs OAP [95% CI]) by Duration of Illness Group; ITT Analysis Set Subjects



	Hazard Ratio (95% CI)	PP (N=579) Relapsed	PP (N=579) Censored	OAP (N=580) Relapsed	OAP (N=580) Censored
Overall	0.69 (0.56-0.86), p<0.001	146 (25.2%)	433 (74.08%)	191 (32.9%)	389 (67.1%)
0-3-year	0.67 (0.44-1.00), p=0.050	40 (15.8%)	213 (84.2%)	57 (21.7%)	206 (78.3%)
>3-5-year	0.57 (0.35-0.93), p=0.025	27 (19.6%)	111 (80.4%)	40 (29.9%)	94 (70.1%)
>5-year	0.74 (0.55-1.00), p=0.049	78 (41.7%)	109 (58.3%)	94 (51.6%)	88 (48.4%)

Regression analysis of survival data based on a Cox proportional hazards model with factor of age, study, duration of illness, treatment group and interaction of duration of illness and treatment group

FIGURE 3: Kaplan-Meier Plot of Time to First Treatment Failure, Days; ITT Analysis Set Subjects



Overall Log-Rank p-value examines the hypothesis that all time to event distributions are similar

TABLE 2: Incidence of Treatment-Emergent Adverse Events by Preferred Term; ITT Analysis Set

	0–3 Years N=516		>3–5 Years N=272		>5 Years N=369	
	PP N=253	OAP N=263	PP N=138	OAP N=134	PP N=187	OAP N=182
Subjects with TEAE	197 (77.9%)	182 (69.2%)	99 (71.7%)	93 (69.4%)	155 (82.9%)	149 (81.9%)
TEAEs Occurring ≥10% of Patients						
Injection site pain	2 (9.5%)	0	11 (8.0%)	0	31 (16.6%)	0
Nasopharyngitis	14 (5.5%)	15 (5.7%)	14 (10.1%)	6 (4.5%)	12 (6.4%)	13 (7.1%)
Weight increased	47 (18.6%)	46 (17.5%)	17 (12.3%)	22 (16.4%)	24 (12.8%)	13 (7.1%)
Akathisia	21 (8.3%)	14 (5.3%)	6 (4.3%)	10 (7.5%)	20 (10.7%)	14 (7.7%)
Headache	27 (10.7%)	20 (7.6%)	16 (11.6%)	16 (11.9%)	14 (7.5%)	15 (8.2%)
Anxiety	21 (8.3%)	15 (5.7%)	6 (4.3%)	8 (6.0%)	20 (10.7%)	17 (9.3%)
Insomnia	30 (11.9%)	34 (12.9%)	17 (12.3%)	9 (6.7%)	36 (19.3%)	21 (11.5%)
Schizophrenia	21 (8.3%)	27 (10.3%)	9 (6.5%)	9 (6.7%)	9 (4.8%)	16 (8.8%)

Conclusions

This analysis showed that PP provides significant benefits in reducing relapse compared to OAPs, regardless of duration of illness

Furthermore, the findings reinforce the importance of implementing PP earlier in the course of schizophrenia

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

Studies differed in design, including observation time & inclusion/exclusion criteria:

- A longer observation time my have shown greater effects between duration of illness groups
- Unintentional exclusion of individuals due to enrollment hesitancy

There are potential biases inherent in any study, however, the studies had oversight from a scientific committee & independent data monitoring committee

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

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