THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Paliperidone Palmitate Once-Monthly Reduces Risk of Relapse of Psychotic, Depressive, and Manic Symptoms and Maintains Functioning in a Double-Blind, Randomized Study of Schizoaffective Disorder

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DOI Number: 10.4088/JCP.14m09416

List of Supplementary Material for the article

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eAPPENDIX 1

Key Exclusion Criteria and Statistical Analysis

Key Exclusion Criteria

Key exclusion criteria for this study were as follows: positive urine screen for cocaine, opiates, phenylcyclohexylpiperidine, or amphetamines; meeting *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) for major depressive disorder, bipolar disorder, or schizophrenia; meeting criteria for any other Axis I diagnosis except substance abuse; having an Axis II diagnosis of mental retardation or borderline personality disorder; meeting the DSM-IV criteria for substance dependence (except for nicotine and caffeine dependence in the 3 months before the screening visit; having attempted suicide within 12 months before the screening visit or at imminent risk of suicide or violent behavior according to the investigator's clinical judgment; being in a first episode of psychosis (no prior history of psychotic symptoms); having received therapy with both mood stabilizers and antidepressants, or having received therapy with mood stabilizers or antidepressants that have been initiated or changed in dose within 30 days prior to screening.

Statistical Analysis

Efficacy and safety summaries for the double-blind (DB) relapse-prevention phase of the study were based on the DB intention-to-treat (ITT) analysis set, which included all randomized subjects who received at least 1 injection of DB study drug. The primary population for efficacy was the DB ITT analysis set.

Primary Efficacy Endpoint

The primary efficacy endpoint for this study was the time between day 1 of the double-blind period and the first documentation of a relapse during the relapse-prevention phase. The primary efficacy null hypothesis was that there is no difference in the distribution of time-to-relapse between the paliperidone monthly and placebo groups in patients with schizoaffective disorder. Treatment differences for time to relapse were compared using a log-rank test stratified by concomitant medication stratum (treatment with mood stabilizers or antidepressants or no such treatment). The cumulative distribution function of the time-to-relapse was estimated by the Kaplan-Meier method. Frequency counts were also compared for relapse and discontinuations using a Cochran-Mantel-Haenszel (CMH) test stratified by concomitant medication stratum.

The reasons for relapse were summarized. Time-to-relapse between treatment groups was evaluated within each subgroup, treatment with concomitant medications (antidepressants or mood stabilizers) and no concomitant treatment. Risk of relapse for the overall group, subgroup of subjects on monotherapy and adjunctive therapy were also examined using Cox proportional hazards models. In addition, a Cox proportional hazards model was extended to include 3 types of mood events: manic, depressive and mixed. Test of hypotheses for any difference in risk of relapse in mood event types was examined by the Global Competing Risk test. The Cox proportional hazards model was also used to examine differences between treatment groups for psychotic relapses.

Key Secondary Endpoint

The key secondary efficacy variable is the mean change from DB baseline in Personal and Social Performance scale (PSP) score at DB endpoint (month 15). The corresponding null

hypothesis for the key secondary endpoint was that there is no difference in mean change from DB baseline in the PSP score between paliperidone monthly and placebo at endpoint.

The overall type I error rate for testing paliperidone monthly versus placebo for both the primary efficacy endpoint and key secondary efficacy endpoint was controlled at the two-sided .05 significance level using a fixed-sequence gatekeeper approach. Time to first relapse was tested first, followed by change from baseline in PSP. If the null hypothesis corresponding to time to first relapse was rejected, then the PSP would be tested at the 5% level, thus maintaining an overall type I error rate of 5%.

The change from DB baseline in PSP score was analyzed using a mixed-model repeated measures analysis of covariance (ANCOVA) model. Using this model, treatment effects at the month 15 endpoint were estimated based on differences between least-squares (LS) mean. Accompanying 95% confidence intervals for the LS mean differences between paliperidone monthly and placebo were presented. The model included baseline PSP score as a fixed-effect covariate; treatment, concomitant medication stratum (treatment with antidepressants or mood stabilizers or no such treatment), country, and time (scheduled assessment visits) as fixed-effect (categorical) factors, and the interaction between time and treatment. An unstructured matrix was used for the covariance of the within-subject repeated measures.

Additional, supportive, sensitivity analyses (pattern mixture model, tipping-point analysis, and pattern mixture modeling with multiple imputation) were performed to assess the robustness and consistency of findings at the month 15 endpoint.

Pattern Mixture Model: This analysis allows missing data to be missing not at random (MNAR). A repeated measures ANCOVA model for change in PSP included time as a categorical factor, and a factor for completers versus early dropouts, as well as the interaction of completion status by treatment and time.

Tipping-Point Analysis: Analysis of PSP score using an iterative process of worsening last observation carried forward (LOCF) values for only the active treatment group (paliperidone monthly) were implemented.

Pattern Mixture Modeling with Multiple Imputation: The analysis was based on a normal distribution pattern mixture model and multiple imputation for a monotone missing data pattern. Multiple imputation was used to impute the missing data under missing data mechanisms for which the missing data are MNAR, where the MNAR mechanisms reflect increasing departures from missing at random.

In addition, subjects who achieved a PSP score ≥71 versus <70 were identified and summarized. The incidence of PSP responders (PSP score ≥71 versus <70) was compared between active treatment group and placebo. Differences between treatment groups were evaluated based on the CMH mean score test using modified ridit scores, stratifying on concomitant medication stratum and country.

Secondary Efficacy Endpoints

The actual values for Positive and Negative Symptom Scale, Young Mania Rating Scale, Hamilton Rating Scale for Depression, 21-item version, Clinical and Global Impression of Severity for Schizoaffective Disorder (CGI-S-SCA) scores were summarized for both open-label (OL) and DB phases using the LOCF data in figures. The treatment group differences in the DB phase were analyzed using an ANCOVA model at endpoint. The model included treatment, concomitant medication stratum (treatment with antidepressants or mood stabilizers or no such treatment), and country as fixed-effect design factors, and corresponding scale specific baseline score as a covariate. Using this model, treatment effects were estimated based on differences between least-squares (LS) mean. Within treatment group differences for change from baseline were evaluated using a paired t-test.

Percentages of subjects reporting each CGI-S-SCA and Medication Satisfaction Questionnaire levels were summarized for both OL and DB phases. Differences between treatment groups was evaluated based on the CMH mean score test using modified ridit scores, stratifying on concomitant medication stratum and country in the DB phase.

Supplementary eFigure 1: Arithmetic Mean (95% CI) PSP Score Over Time Using LOCF Visits

Horizontal line indicates threshold of good functioning, PSP score = 70.

Abbreviations: CI = confidence interval, DB = double-blind, LOCF = last observation carried forward, OL = open-label, PSP = Personal and Social Performance scale.

Supplementary eFigure 2. Secondary Endpoints

(A) PANSS total score; (B) HDRS-21 total score; (C) CGI-S-SCA total score (D), YMRS total score.

All figures show the arithmetic mean (95% CI) over time using the LOCF in the double-blind ITT analysis set.

Horizonal lines in each panel indicate threshold of stabilization/remission.

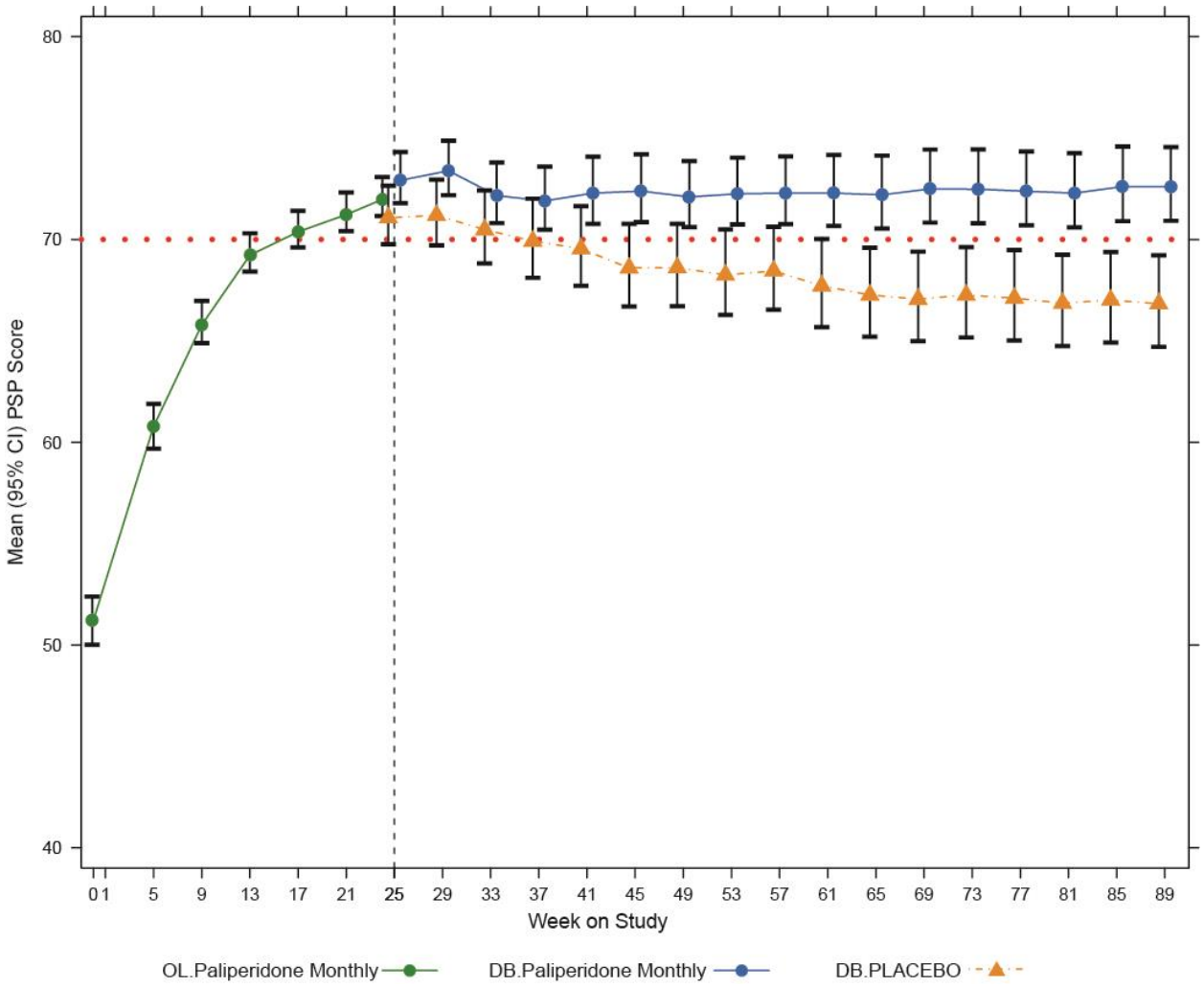
Abbreviations: CGI-S-SCA = Clinical Global Impression of Severity for Schizoaffective Disorder, CI = confidence interval, DB = double-blind, HDRS-21 = Hamilton Rating Scale for Depression, 21-item version, ITT = intention-to-treat, LOCF = last-observation carried forward, OL = open-label, PANSS = Positive and Negative Syndrome Scale, YMRS = Young Mania Rating Scale.

Supplementary eFigure 3. Categorical Changes in CGI-S-SCA (A) and MSQ Scores (B)

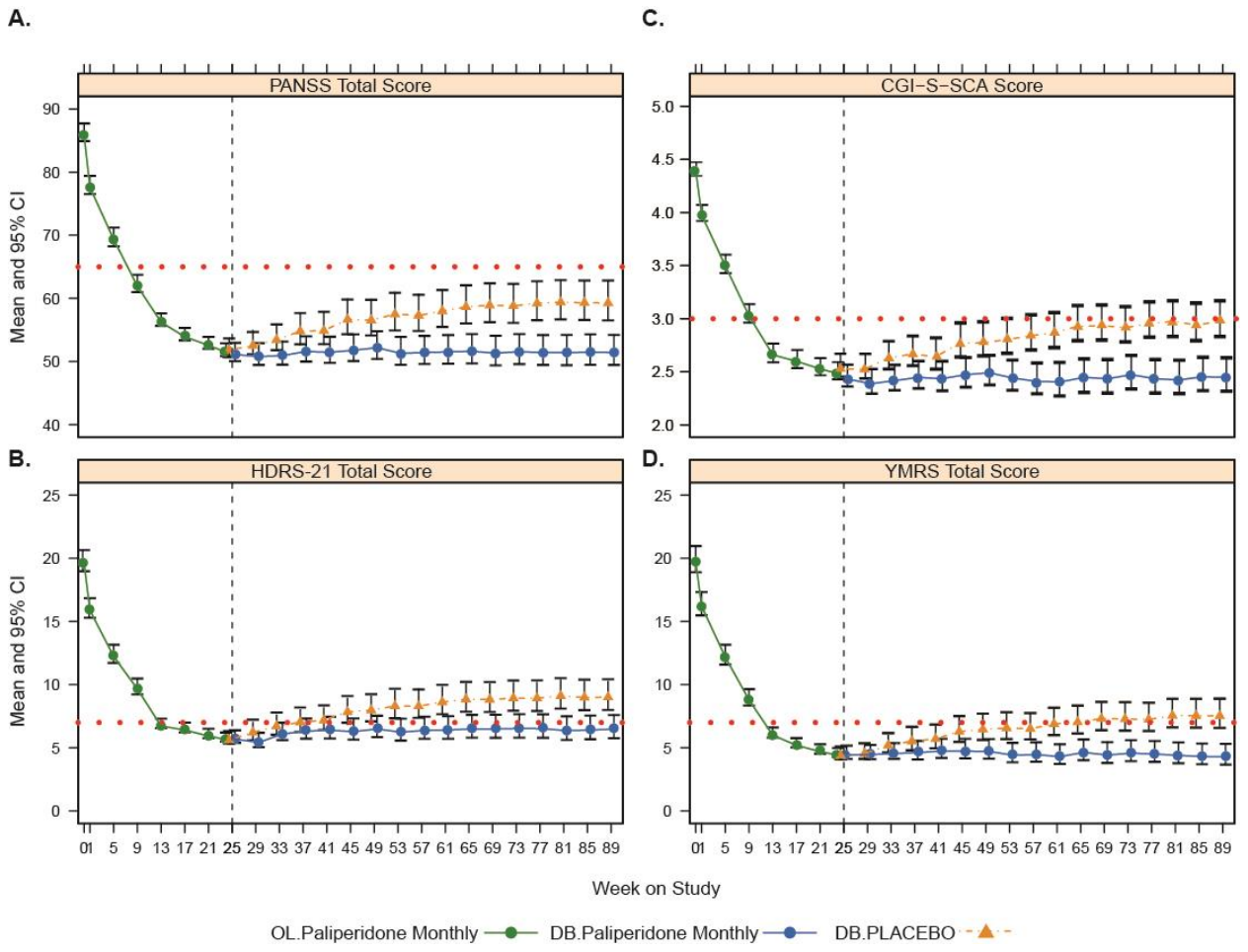
X-Axis = proportion of subjects.

Abbreviations: CGI-S-SCA = Clinical Global Impression of Severity for Schizoaffective Disorder, DB = double-blind, ITT = intention-to-treat, MSQ = Medication Satisfaction Questionnaire, OL = open-label, PBO = placebo

Supplemental efigure 1



Supplemental efigure 2



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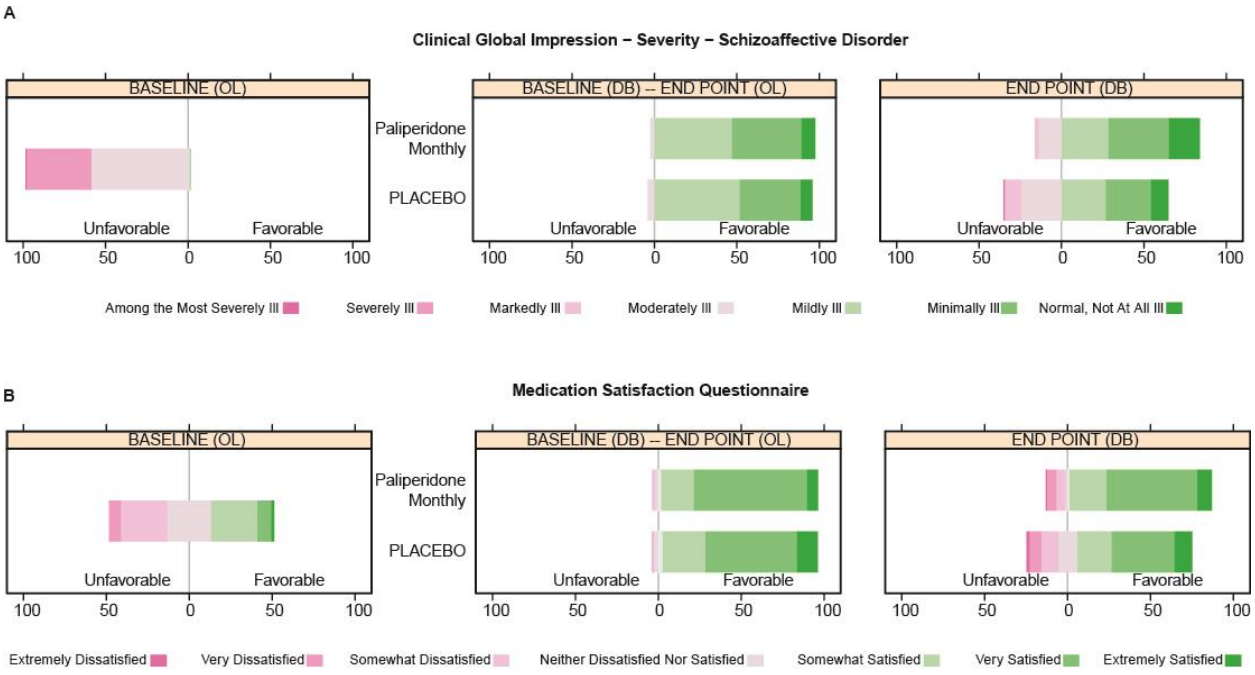

Supplementary eTable 1. Reasons for Relapse in the Double-Blind, Relapse-Prevention Phase

	Placebo (N=170) n (%)	Paliperidone Monthly (N=164) n (%)	All Double-Blind (N=334) n (%)
Number of subjects with relapse	57 (33.5)	25 (15.2)	82 (24.6)
Reasons for relapse			
Psychiatric hospitalization	12 (7.1)	5 (3.0)	17 (5.1)
Interventions employed to avert hospitalizations	23 (13.5)	9 (5.5)	32 (9.6)
Deliberate self-injury, suicidal or homicidal ideation	3 (1.8)	4 (2.4)	7 (2.1)
Self-injury	1 (0.6)	0	1 (0.3)
Suicide attempt	0	0	0
Suicidal ideation	3 (1.8)	4 (2.4)	7 (2.1)
Homicidal ideation	1 (0.6)	1 (0.6)	2 (0.6)
Violent behavior resulting in property damage	0	0	0
Worsening of PANSS items	10 (5.9)	3 (1.8)	13 (3.9)
Worsening of clinical scores at 2 consecutive visits	25 (14.7)	10 (6.1)	35 (10.5)
≥25% increase in PANSS total score	16 (9.4)	5 (3.0)	21 (6.3)
≥10-point increase in PANSS total score when baseline score was ≤45	7 (4.1)	5 (3.0)	12 (3.6)
Worsening of PANSS items	6 (3.5)	4 (2.4)	10 (3.0)
Increase in CGI-S-SCA overall score	12 (7.1)	5 (3.0)	17 (5.1)

Note that subjects could have more than one reason for relapse.

Abbreviations: CGI-S-SCA = Clinical Global Impression of Severity for Schizoaffective Disorder, ITT = intention-to-treat, PANSS = Positive and Negative Syndrome Scale.

Supplementary eTable 2. PSP: LS Mean Differences at Study Endpoint

Method	LS Mean Treatment Difference (SE)	*P* value	95% CI
MMRM[a], month 15	3.3 (1.33)	.014	0.68, 5.95
PMM, month 15	2.1 (1.32)	.105	–0.44, 4.73
PMM without covariate baseline score	3.3 (1.46)	.023	0.44, 6.16
LOCF, tipping point	4.5 (1.32)	<.001	1.94, 7.15
Worsening relapsed paliperidone monthly subjects by 5%	4.1 (1.36)	.002	1.47, 6.80
Worsening relapsed paliperidone monthly subjects by 10%	3.7 (1.39)	.008	0.98. 6.45
Worsening discontinued paliperidone monthly subjects by 5%	3.3 (1.36)	.016	0.63, 5.97
Worsening discontinued paliperidone monthly subjects by 10%	2.0 (1.40)	.145	–0.71, 4.80
Multiple imputation, month 15	3.9 (1.72)	.027	0.44, 7.29
Worsening relapsed paliperidone monthly subjects by 5%	3.4 (1.72)	.055	–0.08, 6.79
Worsening discontinued paliperidone monthly subjects by 5%	2.5 (1.71)	.148	–0.91, 5.92

[a]Primary analysis.

Abbreviations: CI = confidence interval, LOCF = last observation carried forward, LS = least squares, MMRM = mixed-model repeated measures, PMM = pattern mixture model, PSP = Personal and Social Performance scale, SE = standard error.