See commentary by Lauriello et al p264

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

Dong-Jing Fu, MD, PhD; Ibrahim Turkoz, PhD; R. Bruce Simonson, BS; David P. Walling, PhD; Nina R. Schooler, PhD; Jean-Pierre Lindenmayer, MD; Carla M. Canuso, MD; and Larry Alphs, MD, PhD

This work may not be copied, distributed, displayed, published, reproduced, transmitted, modified, posted, sold, licensed, or used for commercial purposes. By downloading this file, you are agreeing to the publisher's Terms & Conditions.

ABSTRACT

Objective: Schizoaffective disorder is a complex illness for which optimal treatment is not well established. Results of the first controlled, relapse-prevention study of paliperidone palmitate once-monthly injectable (paliperidone monthly) in schizoaffective disorder are presented.

Method: The study was conducted between September 20, 2010, and October 22, 2013. Patients with schizoaffective disorder (confirmed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders) experiencing acute exacerbation of psychotic and depressive/manic symptoms were stabilized with paliperidone monthly as monotherapy or as adjunctive therapy to mood stabilizers or antidepressants and randomly assigned (1:1) to paliperidone monthly or placebo in a 15-month, double-blind, relapse-prevention phase. Randomization was stratified by administration as monotherapy or adjunctive therapy and by study center. The primary endpoint was time to relapse.

Results: 334 patients were evaluated. Paliperidone monthly significantly delayed time to relapse for psychotic, depressive, and manic symptoms compared with placebo ($P < .001$, log-rank test). Relapse risk was 2.49 times greater for placebo (hazard ratio = 2.49; 95% CI, 1.55 to 3.99; $P < .001$, Cox proportional hazards model). Overall relapse rates were 33.5% for placebo and 15.2% for paliperidone monthly. For monotherapy, relapse risk was 3.38 times greater with placebo ($P = .002$), and for adjunctive treatment it was 2.03 times greater with placebo ($P = .021$). Paliperidone monthly was superior to placebo in maintaining functioning as measured by the Personal and Social Performance scale ($P = .014$, mixed-model repeated-measures analysis). The most common adverse events (placebo, paliperidone monthly) were increased weight (4.7%, 8.5%), insomnia (7.1%, 4.9%), schizoaffective disorder (5.9%, 3.0%), headache (3.5%, 5.5%), and nasopharyngitis (3.5%, 5.5%). Incidence of any extrapyramidal-related adverse event was 7.1% for placebo and 8.5% for paliperidone monthly.

Conclusions: Paliperidone monthly as monotherapy or adjunctive therapy significantly delayed psychotic, depressive, and/or manic relapses; reduced their risk; and better maintained functioning in patients with schizoaffective disorder. Results support the value of maintenance treatment with paliperidone monthly in schizoaffective disorder.

Trial Registration: ClinicalTrials.gov identifier: NCT01193153

J Clin Psychiatry 2015;76(3):253–262

© Copyright 2014 Physicians Postgraduate Press, Inc.

Submitted: *July 28, 2014; accepted November 11, 2014.*
Online ahead of print: *December 5, 2014 (doi:10.4088/JCP.14m09416).*
Corresponding author: *Dong-Jing Fu, MD, PhD, Clinical Development, Janssen Scientific Affairs, 1125 Trenton-Harbourton Rd, Titusville, NJ 08560 (dfu@its.jnj.com).*

As defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*),[1] schizoaffective disorder presents with mixed symptoms of both schizophrenia and affective disorders.[2] It is about one-third as common as schizophrenia, with an estimated lifetime prevalence of 0.3%.[3] Like schizophrenia, onset of schizoaffective disorder is typically in early adulthood; however, consistent diagnosis usually occurs several years following initial recognition of psychiatric illness.[4–7] Persons with schizoaffective disorder experience significant functional impairment[4,8] and higher rates of hospitalization, suicidality, and substance abuse than persons with schizophrenia.[9] Optimal management of schizoaffective disorder requires long-term treatment, and its prognosis is intermediate to that of schizophrenia and affective disorders.[4,8,10,11]

To manage psychotic, depressive, and manic symptoms, schizoaffective disorder is treated with complex pharmacologic regimens that include antipsychotics, mood stabilizers, and antidepressants.[12–14] Only oral paliperidone, administered as monotherapy or adjunctively with mood stabilizers and/or antidepressants, has received regulatory approval for acute treatment of schizoaffective disorder[5–7,15]; however, no widely accepted clinical guidelines for acute or maintenance treatment exist.

Poor treatment adherence is prevalent with schizoaffective disorder,[16–19] contributing to suboptimal treatment response and poorer long-term outcomes.[20,21] Although some individuals with schizoaffective disorder achieve and maintain symptom stability with available oral antipsychotics and mood stabilizers or antidepressants, many have difficulty adhering to a daily oral regimen.[22] Long-acting injectable therapies, such as once-monthly paliperidone palmitate (paliperidone monthly), provide consistent therapeutic plasma concentrations over several weeks, eliminating the need for daily oral medication and facilitating monitoring of treatment adherence.[23,24] Building on efficacy data of oral paliperidone in acute management of schizoaffective disorder,[5,6] this relapse-prevention study was designed to compare paliperidone monthly given as monotherapy or with adjunctive antidepressants or mood stabilizers to placebo in patients with schizoaffective disorder.

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

Clinical Points

- Long-acting injectable antipsychotic therapies, such as paliperidone monthly, may be beneficial to persons with schizoaffective disorder, who often have poor adherence to treatment.
- Results from this controlled, relapse-prevention study showed that paliperidone monthly significantly delayed and reduced the risk of psychotic, depressive, and manic relapses and better maintained functioning in patients with schizoaffective disorder.
- The delay in relapse and reduction in relapse risk were similar when paliperidone monthly was administered as monotherapy or as adjunctive therapy to mood stabilizers or antidepressants.

METHOD

Study Design

This randomized, double-blind, placebo-controlled, international study of relapse prevention in schizoaffective disorder with paliperidone monthly treatment (ClinicalTrials.gov identifier NCT01193153; clinical registry number CR016618) was conducted between September 20, 2010, and October 22, 2013. It was designed as a pivotal study for the schizoaffective indication. The study was approved by participating ethics committees/institutional review boards and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects. The highest proportion of subjects were enrolled from the United States.

The study included multiple phases (Figure 1). After initial screening, an open-label phase consisted of a 13-week, flexible-dose, lead-in period and a 12-week, fixed-dose, stabilization period. This phase was followed by a 15-month, double-blind, relapse-prevention phase.

Stabilization criteria included Positive and Negative Syndrome Scale (PANSS)[25] total scores ≤ 70, Young Mania Rating Scale (YMRS)[26] scores ≤ 12, and Hamilton Depression Rating Scale, 21-item version (HDRS-21)[27] scores ≤ 12 by the end of the lead-in period. Symptom stabilization had to be maintained throughout the stabilization period without the need for dose adjustments.

Stable subjects entered the 15-month, double-blind, relapse-prevention phase and were randomly assigned (1:1) to receive either paliperidone monthly or placebo injections. Randomization was stratified by absence or presence of mood stabilizers or antidepressants (ie, by monotherapy or adjunctive therapy) and study center. Subjects continued to receive double-blind treatment until predefined relapse, discontinuation, or completion of 15 months. Results of this double-blind phase are the focus of this report.

Study Population

Subjects were required to have a lifetime and current diagnosis of schizoaffective disorder according to the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID) (Clinician Version)[28] conducted during screening. Men and women aged ≥ 18 years with an acute exacerbation of psychotic symptoms ≥ 4 days and ≤ 4 weeks in duration before screening and willing to accept long-acting injectable treatment were eligible. To ensure recruitment of patients who were experiencing exacerbation of psychotic symptoms, subjects had to have a score of ≥ 4 (moderate) on ≥ 3 of the following PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P4 (excitement), P6 (suspiciousness/persecution), P7 (hostility), G4 (tension), G8 (uncooperativeness), or G14 (poor impulse control). Subjects were also required to have prominent mood symptoms (YMRS and/or HDRS-21 scores ≥ 16) at screening. (See eAppendix 1 at PSYCHIATRIST.COM for an outline of key exclusion criteria.)

Treatments

All subjects received intramuscular injections of paliperidone monthly during the 25-week open-label treatment phase. Prestudy antipsychotic therapy was discontinued before the first injection. No oral supplementation was allowed during the study. Subjects entering the double-blind phase received either a fixed dose of paliperidone monthly or matching placebo once every 4 weeks. Paliperidone monthly initiation and dosing are described in Figure 1. Concomitant antidepressants, mood stabilizers, and benzodiazepines were allowed at prestudy stable doses. Limited use of newly started benzodiazepine and nonbenzodiazepine hypnotics was permitted. Subjects were required to be adherent to the study medication, and they were withdrawn from the study if more than 6 weeks had elapsed since the time of their last injection. Sites were permitted to contact patients to remind them of their scheduled visits.

Assessments

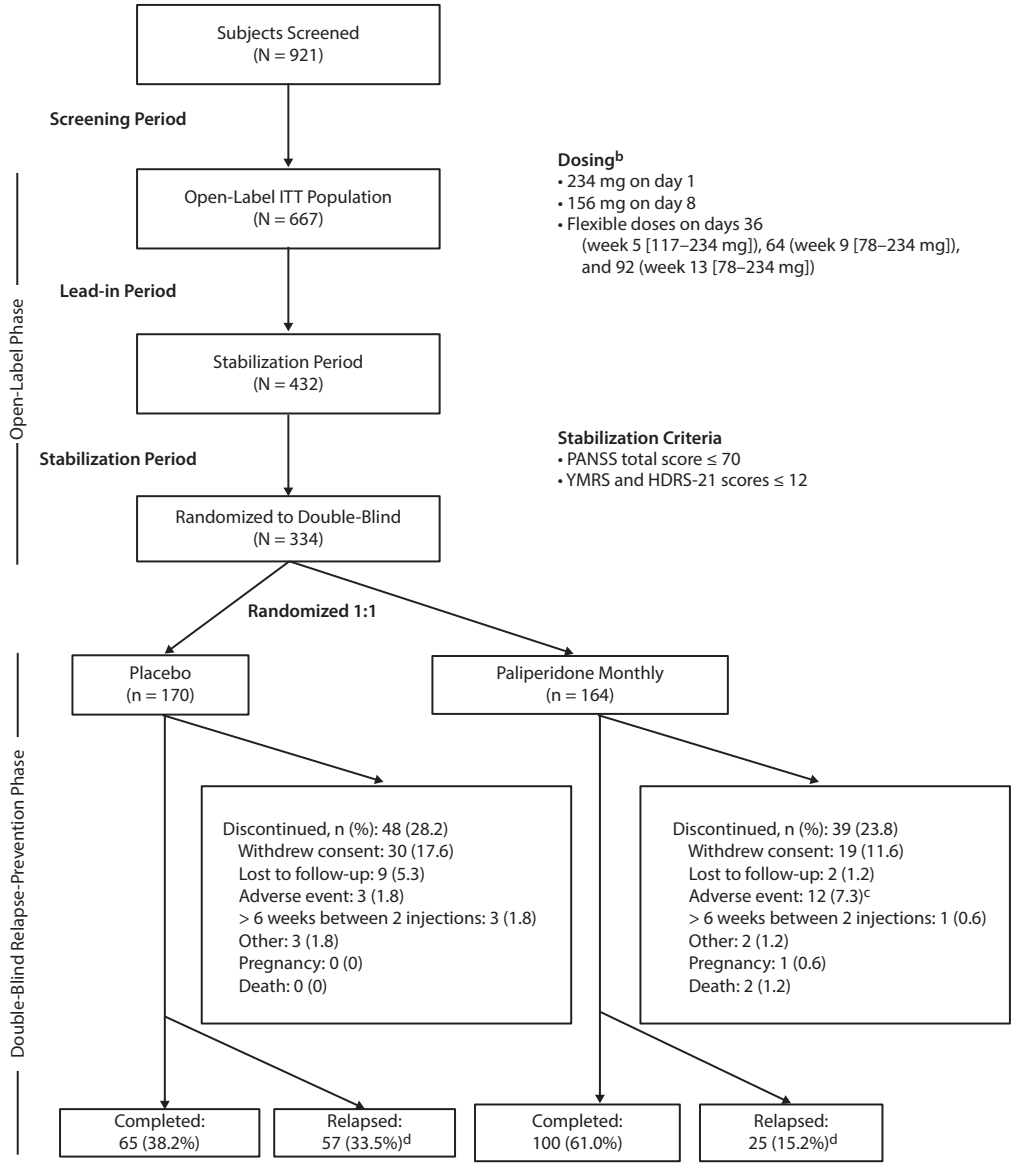
The primary objectives were to evaluate the efficacy of paliperidone monthly compared with placebo in delaying relapse of psychotic, depressive, and/or manic symptoms and to assess safety and tolerability. The definition for relapse used in the study is provided in Figure 1 and included criteria that would identify an impending relapse. The treatment effect of paliperidone monthly versus placebo was evaluated as monotherapy and adjunctive therapy.

The predefined key secondary objective was to evaluate the effect of paliperidone monthly on subject functioning as measured by the Personal and Social Performance scale (PSP).[29,30] Functioning during the month prior to assessment was determined for each of the 4 PSP domains: socially useful activities, personal/social relationships, self-care, and disturbing/aggressive behavior.

Measures of symptomatic change included the PANSS, YMRS, and HDRS-21 total scores. Illness severity was assessed on the Clinical Global Impression of Severity for Schizoaffective Disorder (CGI-S-SCA).[31] The Medication Satisfaction Questionnaire (MSQ)[32] was assessed as a patient-reported outcome. Only qualified raters who are

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

Figure 1. Study Design and Subject Disposition[a]



[a]The study consisted of a 7-day screening period, a 25-week open-label phase (which included a 13-week, open-label, flexible-dose, lead-in period and a 12-week, open-label, fixed-dose, stabilization period), and a 15-month, double-blind, relapse-prevention phase. Subjects without previous exposure to any formulation of risperidone or paliperidone were required to undergo an oral tolerability test.

[b]Dose adjustments were stepwise. Paliperidone monthly doses can be expressed as milligram equivalents (mg eq) of paliperidone or as milligrams (mg) of paliperidone monthly. 50, 75, 100, and 150 mg eq of the active fraction of paliperidone = 78, 117, 156, and 234 mg paliperidone monthly, respectively.

[c]Three of the 12 subjects had treatment-emergent adverse events that developed during the open-label phase, but the subjects did not discontinue the study until the double-blind phase.

[d]Relapse was defined as first occurrence of any 1 of the following:

- Psychiatric hospitalization due to worsening of symptoms
- Any intervention employed to avert imminent hospitalization due to worsening of symptoms (ie, increase in the level of psychiatric care from office visit to day hospitalization [not including increased level of care for social reasons] or the need for additional antipsychotics, antidepressants, or mood stabilizers)
- Clinically significant self-injury, suicidal or homicidal ideation, or violent behaviors
- Worsening of any 1 or more of the following PANSS items to a score ≥ 6 after randomization if the score was ≤ 4 at randomization: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P4 (excitement), P6 (suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness), or G14 (poor impulse control)
- Worsening, as specified below, in any of the following measures at 2 consecutive visits within 7 days:
  - ≥ 25% increase in PANSS total score from randomization if the score at randomization was > 45
  - ≥ 10-point increase in PANSS total score from randomization if the score at randomization was ≤ 45
  - Worsening of any 1 or more of the following PANSS items to a score ≥ 5 after randomization if the score on the corresponding item was ≤ 3 at randomization: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P4 (excitement), P6 (suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness), or G14 (poor impulse control)
  - Increase in CGI-S-SCA ≥ 2 points if the score at randomization was 1 (not ill) to 3 (mildly ill) OR increase ≥ 1 point if the score at randomization was ≥ 4 (moderately ill or worse)

Abbreviations: CGI-S-SCA = Clinical Global Impression of Severity for Schizoaffective Disorder; HDRS-21 = Hamilton Depression Rating Scale, 21-item version; ITT = intent-to-treat; PANSS = Positive and Negative Syndrome Scale; YMRS = Young Mania Rating Scale.

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

trained professionals were allowed to administer the SCID, PANSS, YMRS, HDRS-21, CGI-S-SCA, and PSP.

Statistics

The intent-to-treat (ITT) population was defined as all randomized subjects who received at least 1 injection of double-blind study drug. This population was used for efficacy and safety analyses. Time to first relapse was assumed to follow an exponential distribution with a hazard ratio (HR) of 1.96. With this assumption, ≥ 286 subjects were to be randomly assigned in a 1:1 ratio to paliperidone monthly or placebo to obtain ≥ 95 relapses in order to show whether treatment was significantly different from placebo at a 2-sided significance level of .05, with 90% power to detect an HR of 1.96.

The primary efficacy endpoint was time between day 1 of the double-blind phase and first documentation of relapse. Treatment differences for relapse were evaluated using a log-rank test stratified by concomitant medication stratum (mood stabilizers/antidepressants or no concomitant treatment). A cumulative distribution function of time to relapse was estimated by the Kaplan-Meier method. Risk of relapse for the subgroup of subjects on monotherapy and adjunctive therapy was 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.[33] The Cox proportional hazards model was also used to examine differences between treatment groups for psychotic relapses. Details of analytic methods are described in eAppendix 1.

Mean change from double-blind baseline in PSP score at endpoint (month 15) was the predefined key secondary efficacy variable. Change in PSP score was analyzed using a mixed-model repeated-measures (MMRM) analysis of covariance model. Additional sensitivity analyses were performed to assess the robustness and consistency of findings at double-blind endpoint. Biases associated with missing data were carefully considered. Control of overall Type I error for testing treatment versus placebo for the primary efficacy endpoint and key secondary endpoint and statistical analysis of other secondary efficacy endpoints are described in eAppendix 1.

The number of subjects with ≥ 1 adverse event for each preferred term was summarized regardless of severity and relationship to study medication. Relative risk and corresponding 95% confidence intervals (CIs) associated with these treatment-emergent adverse events (TEAEs) are provided.

RESULTS

Subjects and Disposition

Subject disposition is summarized in Figure 1. A total of 667 subjects were enrolled in the 25-week open-label phase, and 334 were stabilized and subsequently randomized to placebo (n = 170) or paliperidone monthly (n = 164) in the double-blind relapse-prevention phase.

Overall baseline demographics and clinical characteristics were consistent across treatment groups for both enrolled and randomized subjects. Clinical symptom scores improved considerably during 25-week open-label treatment. The mean (SD) open-label baseline scores in this acutely ill population were PANSS, 85.8 (12.76); PSP, 51.4 (11.02); CGI-S-SCA overall, 4.4 (0.58); HDRS-21, 20.4 (7.81); and YMRS, 18.6 (9.48). At study entry, 30.0% of subjects were inpatients, and 24.3% had a history of suicide attempt (Table 1). Percentages of subjects using concomitant antidepressants, mood stabilizers, benzodiazepine and nonbenzodiazepine hypnotics, and anxiolytics were 23.5%, 33.5%, 11.2%, and 17.6%, respectively, in the placebo group and 23.2%, 29.3%, 9.1%, and 18.9%, respectively, in the paliperidone monthly group.

Of 334 randomized subjects, 82 (24.6%) experienced relapse, 165 (49.4%) completed the entire 15-month double-blind phase without relapse, and 87 (26.0%) discontinued the study early for reasons other than relapse (Figure 1). The most common reason for discontinuation was withdrawal of consent. All-cause discontinuations for the placebo and paliperidone monthly groups were 61.8% and 39.0% ($P < .001$, Cochran-Mantel-Haenszel [CMH] test), respectively. Time to all-cause discontinuation in the double-blind phase was significantly shorter for placebo than paliperidone monthly ($P < .001$). Monthly dosing distribution during the double-blind phase was 4.9% of subjects at 78 mg, 9.8% at 117 mg, 47.0% at 156 mg, and 38.4% at 234 mg. Median duration of exposure was 268.5 and 446.0 days for the placebo and paliperidone monthly groups, respectively.

Efficacy

Paliperidone monthly treatment was associated with significant delay in time to relapse compared with placebo ($P < .001$) using the log-rank test controlling for concomitant medication strata (with or without adjunctive mood stabilizers/antidepressants) (Figure 2). Correspondingly, a significantly lower percentage of subjects treated with paliperidone monthly experienced a relapse event ($P < .001$, CMH test), with relapse rates of 33.5% (n = 57) and 15.2% (n = 25) in the placebo and paliperidone monthly groups, respectively. Relapse risk in the double-blind phase was 2.49-fold higher for placebo compared with paliperidone monthly (HR = 2.49; 95% CI, 1.55 to 3.99; $P < .001$), corresponding to a 60% decrease in relapse risk with maintenance treatment (Table 2).

Relapse risk was significantly higher for placebo versus paliperidone monthly in both monotherapy (HR = 3.38; $P = .002$) and adjunctive therapy (HR = 2.03; $P = .021$) subgroups. For the monotherapy subgroup, 32.9% (n = 24) and 11.5% (n = 9) of placebo and paliperidone monthly subjects, respectively, experienced a relapse. For the adjunctive therapy subgroup, relapse rates were 34.0% (n = 33) and 18.6% (n = 16), respectively.

When treatment effect was evaluated by relapse type, relapse risk was significantly higher for placebo versus

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY OR COMMERCIAL PURPOSES.

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Open-Label Phase (N = 667)	Double-Blind Phase		
		All Subjects (N = 334)	Placebo (n = 170)	Paliperidone Monthly (n = 164)
Age, mean (range), y	39.5 (19–66)	38.6 (19-66)	38.0 (19-66)	39.3 (19-65)
Male, n (%)	357 (53.5)	169 (50.6)	84 (49.4)	85 (51.8)
Race, n (%)				
White	354 (53.1)	183 (54.8)	88 (51.8)	95 (57.9)
Black/African American	195 (29.2)	72 (21.6)	43 (25.3)	29 (17.7)
Asian	108 (16.2)	74 (22.2)	37 (21.8)	37 (22.6)
Other	10 (1.5)	5 (1.5)	2 (1.2)	3 (1.8)
BMI, mean (SD), kg/m^2	27.88 (5.58)	27.25 (5.64)	27.38 (5.44)	27.12 (5.86)
Duration of illness, n (%)[a]				
≤ 5 y	206 (30.9)	119 (35.6)	60 (35.3)	59 (36.0)
> 5 y	461 (69.1)	215 (64.4)	110 (64.7)	105 (64.0)
Age, mean (SD), y at:				
First psychiatric diagnosis	26.1 (9.8)	26.4 (9.4)	25.7 (9.3)	27.1 (9.4)
First schizoaffective diagnosis	31.5 (10.3)	30.9 (10.1)	30.3 (10.2)	31.5 (10.1)
First pharmacologic treatment for psychiatric symptoms	26.6 (9.8)	26.7 (9.3)	26.2 (9.2)	27.2 (9.4)
Schizoaffective subtype, n (%)				
Depressive	237 (35.5)	101 (30.2)	59 (34.7)	42 (25.6)
Bipolar	430 (64.5)	233 (69.8)	111 (65.3)	122 (74.4)
Previous psychiatric diagnosis, n (%)[b]				
Bipolar disorder	147 (22.0)	68 (20.4)	37 (21.8)	31 (18.9)
Depression	142 (21.3)	53 (15.9)	25 (14.7)	28 (17.1)
Schizoaffective disorder	660 (99.0)	332 (99.4)	170 (100.0)	162 (98.8)
Schizophrenia	170 (25.5)	80 (24.0)	39 (22.9)	41 (25.0)
Attempted suicide, n (%)	162 (24.3)	60 (18.0)	32 (18.8)	28 (17.1)
History of substance use, n (%)	247 (37.0)	90 (26.9)	44 (25.9)	46 (28.0)
No. of psychiatric hospitalizations, mean (SD)	4.8 (8.24)	3.9 (4.74)	4.0 (5.04)	3.8 (4.43)
Inpatient at study entry, n (%)	200 (30.0)	105 (31.4)	47 (27.6)	58 (35.4)
Concomitant antidepressants, n (%)	161 (24.1)	78 (23.4)	40 (23.5)	38 (23.2)
Concomitant mood stabilizers, n (%)	186 (27.9)	105 (31.4)	57 (33.5)	48 (29.3)
Current episode at study entry, n (%)				
Psychotic symptoms	667 (100.0)	334 (100.0)	170 (100.0)	164 (100.0)
Mood symptoms	667(100.0)	334 (100.0)	170 (100.0)	164 (100.0)
Manic	179 (26.8)	109 (32.6)	51 (30.0)	58 (35.4)
Depressive	320 (48.0)	147 (44.0)	84 (49.4)	63 (38.4)
Mixed	168 (25.2)	78 (23.4)	35 (20.6)	43 (26.2)
Baseline scores at start of study phase,[c] mean (SD)				
PSP	51.4 (11.02)	72.0 (8.97)	71.1 (9.56)	72.9 (8.24)
PANSS	85.8 (12.76)	51.5 (9.47)	51.8 (9.47)	51.1 (9.50)
CGI-S-SCA overall	4.4 (0.58)	2.5 (0.69)	2.5 (0.69)	2.4 (0.68)
HDRS-21	20.4 (7.81)	5.7 (3.28)	5.6 (3.32)	5.7 (3.24)
YMRS	18.6 (9.48)	4.4 (3.42)	4.4 (3.40)	4.4 (3.46)

[a]Since first psychiatric diagnosis.
[b]Data are not mutually exclusive.
[c]Baseline scores are those measured at the start of each study phase (either at the start of the open-label phase in which all subjects received paliperidone monthly or at the start of the double-blind relapse-prevention phase in which subjects stabilized on paliperidone monthly in the open-label phase were randomized to receive paliperidone monthly or placebo).
Abbreviations: BMI = body mass index; CGI-S-SCA = Clinical Global Impression of Severity for Schizoaffective Disorder; HDRS-21 = Hamilton Depression Rating Scale, 21-item version; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance Scale; SD = standard deviation; YMRS = Young Mania Rating Scale.

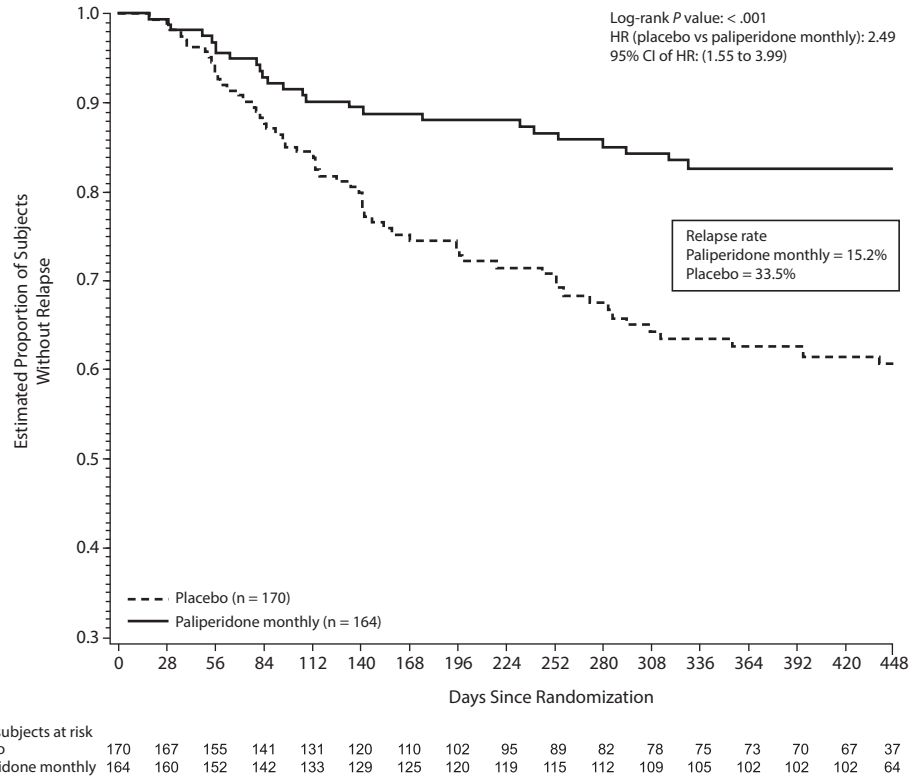
paliperidone monthly in subjects with psychotic ($P < .001$), depressive ($P = .006$), or manic ($P = .012$) relapse. The risk ratio for relapse favoring treatment did not differ across different mood episode types ($P = .718$, Global Competing Risk test).

The most common reasons for relapse across both treatment groups were worsening of clinical symptom scores and interventions to avert hospitalizations (ie, increase in the level of psychiatric care from office visit to day hospitalization [not including increased level of care for social reasons] or the need for additional antipsychotics, antidepressants, or mood stabilizers) (Supplementary eTable 1). Hospitalization for decompensating schizoaffective disorder symptoms occurred in 7.1% of subjects in the placebo group and 3.0% in the paliperidone monthly group.

Mean change in PSP from baseline at month 15 significantly favored paliperidone monthly over placebo ($P = .014$) using MMRM analysis, and the least squares mean difference between groups in change scores at month 15 was 3.3 (95% CI, 0.68 to 5.95) (Supplementary eFigure 1). To evaluate the validity of the missing-at-random assumption for PSP, several sensitivity analyses based on missing-not-at-random were performed to assess robustness and consistency of findings at the month 15 endpoint. These analyses confirmed that paliperidone monthly was superior to placebo for maintaining functioning as measured by PSP at endpoint (Supplementary eTable 2).

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

Figure 2. Kaplan-Meier Curves of Estimated Time to Relapse[a]



[a]Day 0 denotes baseline of the double-blind phase.
Abbreviations: CI = confidence interval, HR = hazard ratio.

Table 2. Hazard Ratio of Relapse

	Placebo, Event/n (%)	Paliperidone Monthly, Event/n (%)	Risk of Relapse (placebo vs paliperidone monthly)[a]	95% CI of Risk of Relapse	*P* Value
All subjects	57/170 (33.5)	25/164 (15.2)	2.49	1.55 to 3.99	< .001
Monotherapy	24/73 (32.9)	9/78 (11.5)	3.38	1.57 to 7.28	.002
Adjunctive to antidepressants or mood stabilizers	33/97 (34.0)	16/86 (18.6)	2.03	1.11 to 3.68	.021
Antidepressants	15/40 (37.5)	7/38 (18.4)	2.38	0.97 to 5.86	.058
Mood stabilizers	18/57 (31.6)	9/48 (18.8)	1.78	0.80 to 3.98	.157
Psychotic symptoms[b]	53/170 (31.2)	21/164 (12.8)	2.82	1.70 to 4.67	< .001
Mood symptoms[c]	48/170 (28.2)	18/164 (11.0)	2.93	1.70 to 5.04	< .001
Depressive	23/170 (13.5)	8/164 (4.9)	3.12	1.39 to 6.98	.006
Manic	16/170 (9.4)	5/164 (3.0)	3.62	1.32 to 9.89	.012
Mixed	9/170 (5.3)	5/164 (3.0)	1.93	0.65 to 5.78	.238

[a]The instantaneous risk (hazard) of relapse for placebo-treated subjects compared to subjects treated with paliperidone monthly. Risk of relapse, corresponding *P* values, and 95% CIs are from separate Cox proportional hazards regression models.
[b]8 subjects experienced a relapse without psychotic symptoms.
[c]16 subjects experienced a relapse with no mood symptoms.
Abbreviation: CI = confidence interval.

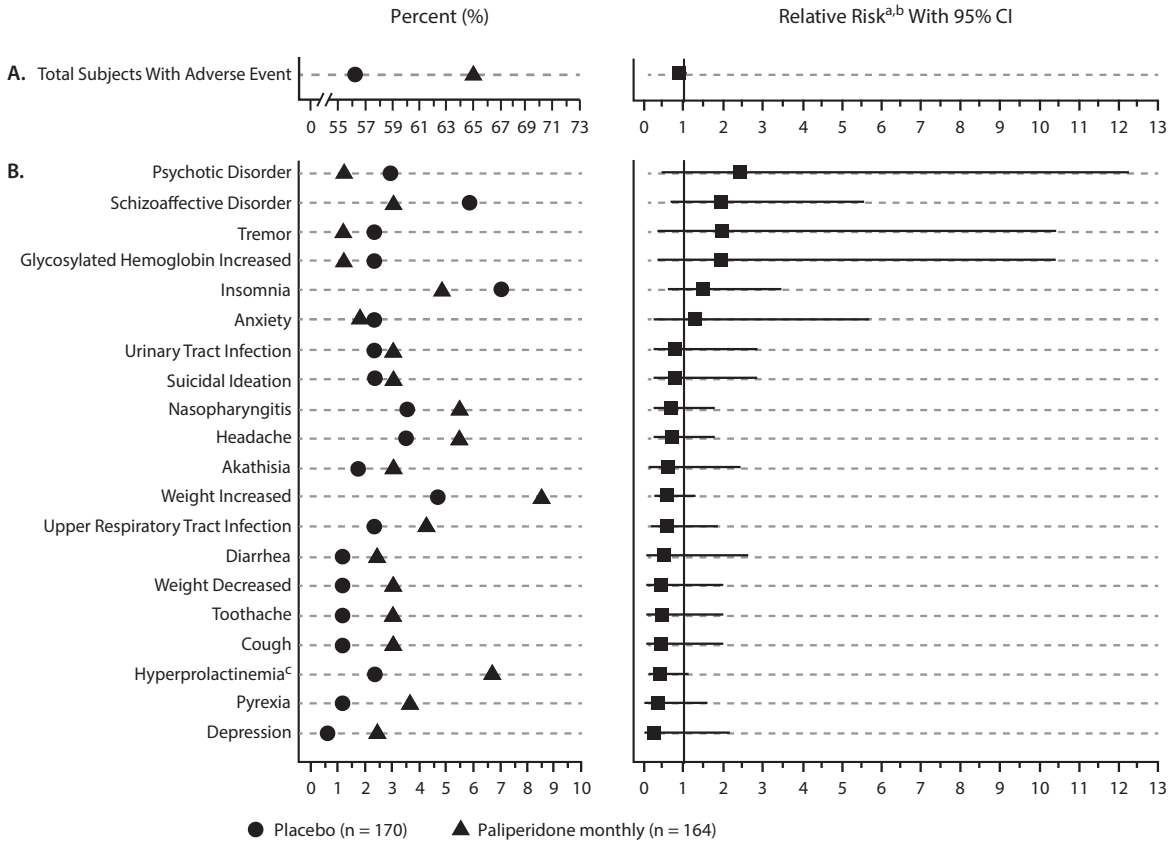
To further evaluate the clinical relevance and consistency of PSP results, subject-level PSP data were examined as a categorical endpoint. The proportion of placebo-treated subjects with good functioning (PSP total score > 70) was 50.6% at double-blind baseline and 41.1% at endpoint, whereas it was 57.9% at double-blind baseline and 59.0% at endpoint (between-group difference, $P = .002$) for paliperidone monthly treated subjects with good functioning.

Additional secondary efficacy analyses are summarized in Supplementary eFigure 2. The LS-mean between-group differences for change in HDRS-21, YMRS, PANSS, and CGI-S-SCA total scores all significantly favored paliperidone monthly over placebo: HDRS-21 total scores: –2.5; 95% CI, –3.93 to –1.12; $P < .001$; YMRS total scores: –3.2; 95% CI, –4.53 to –1.83; $P < .001$; PANSS total scores: –6.9; 95% CI, –10.41 to –3.37; $P < .001$; CGI-S-SCA scores: –0.5; 95% CI, –0.69 to –0.24; $P < .001$.

The proportions of subjects with CGI-S-SCA scores of "not ill" to "mildly ill" at double-blind baseline were 95.9% (88/170) and 97.6% (74/164) for the placebo and paliperidone monthly groups, respectively. These percentages decreased at double-blind endpoint to 64.9% (45/168)

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

Figure 3. Summary of Common TEAEs (≥ 2% in either treatment group)



[a]Placebo vs paliperidone monthly.
[b]Relative risk value > 1 indicates greater risk of TEAEs with placebo, and < 1 indicates greater risk with paliperidone monthly.
[c]The term *blood prolactin increased* included with the adverse event term *hyperprolactinemia*.
Abbreviations: CI = confidence interval, TEAE = treatment-emergent adverse event.

and 83.9% (46/161), respectively (between-group difference, $P < .001$) (Supplementary eFigure 3A).

The proportion of subjects who were satisfied with their antipsychotic medication per the MSQ scale favored paliperidone monthly treatment: for placebo (93.5% of subjects at double-blind baseline and 69.6% at endpoint) compared with paliperidone monthly (94.5% at double-blind baseline and 85.7% at endpoint) (between-group difference, $P < .001$) (Supplementary eFigure 3B).

Safety

Common TEAEs reported during the double-blind phase are shown in Figure 3. Most TEAEs were mild to moderate. The most common (≥ 5% incidence in either treatment group) included schizoaffective disorder (placebo vs paliperidone monthly: 5.9%, 3.0%), weight increased (4.7%, 8.5%), nasopharyngitis (3.5%, 5.5%), headache (3.5%, 5.5%), and insomnia (7.1%, 4.9%). Serious TEAEs were reported in 9.4% and 5.5% of subjects in the placebo and paliperidone monthly groups, respectively, with events related to psychiatric disorders the most frequent. Two deaths occurred in the paliperidone monthly group. These included 1 death due to overdose of sleeping pills and another due to coronary artery disease. Both deaths were assessed by the investigator as not related to study drug. Three subjects (1.8%) in the placebo group discontinued therapy because of TEAEs (Ménière's disease, hepatitis C, and insomnia), while 12 subjects (7.3%) in the paliperidone monthly group discontinued due to TEAEs (cardiac failure congestive, fatigue, blood glucose increased, weight increased, musculoskeletal stiffness, akathisia, schizoaffective disorder, galactorrhea [2 patients], dermatitis, cognitive disorder, and abdominal discomfort). No significant differences between treatment groups in TEAE incidence were identified (ie, the CI of the relative risk values consistently crossed the boundary of 1).

Rates of extrapyramidal symptom (EPS)–related TEAEs were 7.1% in the placebo group and 8.5% in the paliperidone monthly group. Specific events included hyperkinesia (2.9%, 3.7%), parkinsonism (1.8%, 3.0%), tremor (2.4%, 1.2%), dyskinesia (1.8%, 0.6%), and dystonia (1.2%, 0). The percentage of subjects using anti-EPS medications at any time during double-blind treatment was 18.8% in the placebo group and 18.9% in the paliperidone monthly group.

Prolactin-related TEAEs were reported in 5.8% of women who received placebo and in 13.9% receiving paliperidone monthly; the most common were hyperprolactinemia/blood prolactin increase (3.5%, 8.9%), amenorrhea (2.3%, 3.8%), and galactorrhea (1.2%, 3.8%). Prolactin-related

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

TEAEs were reported in 1.2% of men receiving placebo and 7.1% receiving paliperidone monthly; the most common of these was hyperprolactinemia/blood prolactin increase (0%, 4.7%).

Glucose-related TEAEs occurred in 2.4% of subjects receiving placebo and in 1.8% receiving paliperidone monthly. The proportion of subjects with a ≥ 7% weight increase was 6.0% for placebo and 13.0% for paliperidone monthly. The mean (SD) weight change was –0.8 (4.5) kg and –0.2 (6.1) kg for placebo and paliperidone monthly subjects, respectively.

DISCUSSION

This double-blind study supports the efficacy and safety of paliperidone monthly when used as monotherapy or adjunctive therapy for maintenance treatment of schizoaffective disorder. Withdrawal of treatment for patients in the placebo group previously stabilized on paliperidone monthly treatment resulted in a 2.49-fold increased relapse risk compared to continued treatment with paliperidone monthly, supporting a protective effect in the schizoaffective disorder population at high risk for poor adherence and relapse into psychosis, depression, and/or mania. Consistent with this potential benefit of paliperidone monthly therapy, the median duration of exposure during the 15 months of observation was 160 days longer with continued treatment compared with withdrawal to placebo. These findings extend observations from schizophrenia trials[34] demonstrating the ability of paliperidone monthly to maintain efficacy for psychosis and support maintenance effects for preventing emergence of depression and mania symptoms in schizoaffective disorder. These results support prior evidence that the paliperidone molecule is effective and safe for acute management of these schizoaffective disorder symptoms following relapse.[5,6]

The efficacy of paliperidone monthly monotherapy suggests that it may serve as a foundation for treatment of patients with schizoaffective disorder. As monotherapy, paliperidone monthly eliminates requirements for simultaneous management of multiple psychotropic medications for physicians and daily oral medication adherence by patients. In this study, the effect of treatment appeared smaller with adjunctive therapy, which may reflect partial efficacy of adjunctive treatment and/or more refractory illness in patients requiring adjunctive therapies.

Relapse criteria in this study were designed to identify early indicators of relapse, such as symptom worsening or need for increase in psychotropic medications. These criteria minimized the potential for patients to experience a fully symptomatic relapse. Patients with an impending relapse were immediately discontinued from the study for rapid institution of standard treatment. This study design aspect may have contributed to the relatively small observed treatment effect for some secondary efficacy variables during double-blind treatment phase and differences in changes in overall functioning.

Improving and maintaining patient functioning beyond symptom control is a key long-term treatment goal. The PSP score reflects the composite of 4 functional domains (socially useful activities, personal/social relationships, self-care, and disturbing/aggressive behavior). Results from this study demonstrate that paliperidone monthly better maintains long-term functioning as measured by the PSP, providing potential value beyond maintenance of symptom control. Biases associated with missing PSP data were carefully considered; however, the inherent issue of informative censoring in a relapse-prevention study design may require additional interpretation of the PSP data. Patient experience with medication contributes to adherence. In this study, patient satisfaction was better maintained with paliperidone monthly treatment compared to placebo.

Enrolled subjects had a current and lifetime diagnosis of schizoaffective disorder according to *DSM-IV*. On the basis of investigator assessments following the release of *DSM-5*, 95% of randomized subjects also met *DSM-5* diagnostic criteria for schizoaffective disorder, confirming that the study population represents patients with schizoaffective disorder according to current diagnostic criteria.

The pattern of TEAEs was similar to those reported in the previously conducted maintenance study of paliperidone monthly in schizophrenia,[34] and no new safety concerns were detected. Only patients who could be stabilized on and tolerated treatment were included in the double-blind, placebo-controlled study phase. The 25-week prior open-label treatment with paliperidone monthly may have minimized observations of TEAEs associated with treatment. Tolerability and efficacy findings for the open-label phase of this study will be reported elsewhere.

Consistent with most controlled efficacy studies, a limitation of this study is that the subject population was chosen to minimize confounding factors such as substance dependence. It was also limited to patients who consented to receive long-acting injectable therapy. Therefore, results may not be generalizable to all patients with schizoaffective disorder.

In conclusion, this study provides evidence that paliperidone monthly significantly delayed and reduced risk of relapse of psychotic, depressive, and manic symptoms and better maintains functioning when used as monotherapy or adjunctive therapy in patients with schizoaffective disorder.

Drug names: paliperidone palmitate (Invega Sustenna), risperidone (Risperdal and others).

Author affiliations: Scientific Affairs, Janssen Scientific Affairs, LLC (Drs Fu and Alphs); Biostatistics, Janssen Research & Development, LLC (Dr Turkoz); Global Clinical Operations, Janssen Research & Development, LLC (Mr Simonson); and Central Nervous System, Janssen Research & Development, LLC (Dr Canuso), Titusville, New Jersey; Collaborative Neuroscience Network, Inc, Garden Grove, California (Dr Walling); Department of Psychiatry, SUNY Downstate Medical Center, Brooklyn, New York (Dr Schooler); and Department of Psychiatry, New York University Langone Medical Center, New York (Dr Lindenmayer).

Author contributions: Drs Fu, Walling, Schooler, Lindenmayer, Canuso, and Alphs and Mr Simonson were responsible for study concept and design, analysis and interpretation of the data, drafting of the manuscript, and critical revision of the manuscript. Dr Turkoz was responsible for study concept and design, acquisition of data, analysis and interpretation of the data, statistical analysis of the data, drafting of the manuscript, and critical revision of manuscript for important intellectual content.
All authors have read and approved the final version of the manuscript.

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY OR COMMERCIAL PURPOSES.

Study investigators: The authors thank the following investigators who contributed data to the study: Volodymyr Abramov, MD, PhD, ScD (Donetsk, Ukraine); Neal Adams, MD, MPH, and Ira Glick, MD (Oakland, CA); Maria Alexandrova, MD, PhD (Pleven, Bulgaria); George M. Badescu, MD (Craiova, Romania); Michael D. Banov, MD (Marietta, GA); Vinay L. Barhale, MD (Aurangabad, India); James T. Barker II, MD (Charlotte, NC); Norhayati Binti Nordin, MD (Kota Kinabalu, Malaysia); Yuliya Blazhevych, MD (Kiev, Ukraine); Ronald L. Brenner, MD (Cedarhurst, NY); Joel S. Breving, MD (Staten Island, NY); David W. Brown, MD (Austin, TX); Rowena G. Cosca, MD (Iloilo City, Philippines); Doina C. Cozman, MD (Cluj-Napoca, Romania); Monina G. Cruz, MD (Quezon City, Philippines); Irina A. Dan, MD (Bucharest, Romania); Bethany B. Davis, MD, and Brian S. Bortnick, MD (Atlanta, GA); Temenuzhka Dechkova-Novakova, MD (Ruse, Bulgaria); Vladyslav Demchenko, MD (Kiev, Ukraine); Michael Downing, MD (Dallas, TX); Esther G. Ebenezer, Assoc Prof, MBBS (Ipoh, Malaysia); Tsveteslava Galabova, MD (Novi Iskar, Bulgaria); Hitendra A. Gandhi, MD (Ahmedabad, India); Donald Garcia, Jr, MD (Austin, TX); Eduard Gfeller, MD (Maitland, FL); Elena Gherman, MD (Bucharest, Romania); Liana Giurgiuca, MD (Bucharest Romania); Armen K. Goenjian, MD (Torrance, CA); Gerhard P. Grobler, MD (Pretoria, Republic of South Africa); Daniel Gruener, MD (Philadelphia, PA); Thomas A. Grugle, MD (Dallas, TX); Mariano S. Hembra, MD (Iloilo City, Philippines); Luchezar Hranov, PhD, MD (Sofia, Bulgaria); Vishal India, MD (Andhra, India); Karl Jacobs, MD (San Diego, CA); Suarn Singh Jasmit Singh, MBBS (Tanjung Rambutan, Malaysia); Venu G. Jhanwar, MD (Varanasi, India); Emil Kaludiev, MD, PhD (Sofia, Bulgaria); Mary A. Knesevich, MD (Irving, TX); Joseph Kwentus, MD (Flowood, MS); Maria Ladea, MD (Bucharest, Romania); Olga M. Lapeyra, MD, and Peter P. Ventre, MD (North Miami, FL); Igor Linskiy, MD, PhD, Dr Med Sc (Kharkiv, Ukraine); Jennifer M. Lytle, MD, MPH (Denver, CO); Mirela Manea, MD (Bucharest, Romania); Raymond Manning, MD (Pico Rivera, CA); Gabriela Marian, MD (Bucharest, Romania); Victor Marinescu, MD (Bucharest, Romania); Nataliya Maruta, MD, PhD (Kharkiv, Ukraine); Svitlana Moroz, MD, PhD (Dnipropetrovsk, Ukraine); Paul W. Murphy, MD (Wichita, KS); Unmesh Nagapurkar, MD (Nashik, India); Daniel J. Niehaus, Prof (Cape Town, Republic of South Africa); Anil Nischal, MD (Lucknow, India); Gheorghe Oros, MD (Oradea, Romania); Bogdan M. Pacala, MD (Sibiu, Romania); Agnes B. Padilla, MD (Davao City, Philippines); Pavlo Palamarchuk, MD (Stepanivka, Ukraine); Sanjay Phadke, MD (Pune, India); Delia Podea, MD (Arad, Romania); Stefan Popov, MD (Plovdiv, Bulgaria); Satheesh Rao, MD (Mangalore, India); Sathyanarayana Rao, MBBS, DPM, MD (Mysore, India); Oleksandr Romaniv, MD (Uzhgorod, Ukraine); Sofiya Rymsha, MD, PhD, Dr Med Sc (Vinnytsa, Ukraine); Martha Sajatovic, MD (Cleveland, OH); Ramanathan Sathianathan, MBBS, DPM, MD (Chennai, India); Juan P. Schronen, MD (Cape Town, Republic of South Africa); Scott Segal, MD (Ft. Lauderdale, FL); Sandip H. Shah, MD (Vadodara, India); Rajinder Shiwach, MD, and Ernest Brownlee, Jr, MD (DeSoto, TX); Franco Sicuro, MD (Creve Coeur, MO); Dorina Sima, MD (Bucharest, Romania); Dinesh Singh, MD (Durban, Republic of South Africa); Andrii Skrypnikov, MD, PhD (Poltava, Ukraine); Sherry A. Soefje, MD, and Jelena Kunovac, MD (Oceanside, CA); Mary Stedman, MD (Tampa, FL); Ahamad H. Sulaiman, MBBS (Kuala Lumpur, Malaysia); Rajagopal Sunder, MD; Lily S. Chung, MD; Sadashiv Rajadhyaksha, MD; and Samuel Dey, Jr, MD (Riverside, CA); Simona C. Tamasan, MD (Timisoara, Romania); Anil Tambi, MD (Jaipur, India); Alexandru Tiugan, MD (Craiova, Romania); Mauricio Tohen, MD, DrPH, MBA (San Antonio, TX); Maria Silvi Trandafir, MD (Bucharest, Romania); Tram Tran-Johnson, PharmD, PsyD (San Diego, CA); Jitendra Trivedi, MD (Lucknow, India); Catalina Tudose, MD (Bucharest, Romania); Lidia N. Udangiu, MD (Bucharest, Romania); Daniel Vasile, MD (Bucharest, Romania); Gert J. Venter, MD (Gauteng, Republic of South Africa); Viktoriya Verbenko, MD, PhD (Symferopol, Ukraine); Mykhaylo Vynnyk, MD, PhD, Dr Med Sc (Ivano-Frankovsk. Ukraine); David P. Walling, PhD (Garden Grove, CA); Blaise Wolfrum, MD (Schaumburg, IL); Rakesh Yadav, MD (Jaipur, India); and Gennadii Zilberblat, MD (Glevakha, Ukraine).

Potential conflicts of interest: **Drs Fu** and **Alphs** are employees of Janssen Scientific Affairs, LLC, and Johnson & Johnson stockholders. **Drs Turkoz** and **Canuso** and **Mr Simonson** are employees of Janssen Research & Development, LLC, and Johnson & Johnson stockholders. **Dr Walling** has received grant/research support from Janssen Research Foundation. **Dr Schooler** has received grant/research support from Otsuka, Neurocrine, and Genentech and has served as advisory board member/speaker for Roche, Forum, Sunovion, and Lundbeck. **Dr Lindenmayer** has received grant/research support from Janssen, Eli Lilly, Pfizer, Otsuka, Dainippon Sumitomo, Sunovion, Neurocrine, EnVivo, and Roche and is a consultant for Janssen.

Funding/support: This study was funded by Janssen Scientific Affairs, LLC (Primary Study Protocol Number R092670-SCA-3004), which was responsible for the design and conduct of the study and for the collection, management, analysis, and interpretation of the data. Writing and editorial assistance were also funded by Janssen Scientific Affairs, LLC.

Previous presentations: This work has been presented in part at the American Psychiatric Association 167th Annual Meeting; May 3–7, 2014; New York, New York ▪ Society of Biological Psychiatry 69th Annual Scientific Meeting; May 8–10, 2014; New York, New York ▪ ASCP Annual Meeting; June 16–19, 2014; Hollywood, Florida ▪ XVI World Congress of Psychiatry; September 14–18, 2014; Madrid, Spain ▪ American Psychiatric Nurses Association 28th Annual Conference, October 22–25, 2014; Indianapolis, Indiana ▪ 27th ECNP Congress of Applied and Translational Neuroscience; October 18–21, 2014; Berlin, Germany ▪ Institute on Psychiatric Services Annual Meeting; October 30–November 2, 2014; San Francisco, California.

Acknowledgments: The authors thank Tricia Newell, PhD; Matthew Grzywacz, PhD; and ApotheCom, LLC, Yardley, Pennsylvania, for providing writing and editorial assistance for this manuscript (funded by Janssen Scientific Affairs, LLC). The authors also thank Cynthia A. Bossie, PhD (Janssen Scientific Affairs, LLC), for her scientific input and discussions and Erin Lee, RN (Janssen Scientific Affairs, LLC), for her assistance in data review.

Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. Arlington, VA: American Psychiatric Publishing; 2013.
2. Malaspina D, Owen MJ, Heckers S, et al. Schizoaffective disorder in the *DSM-5*. *Schizophr Res*. 2013;150(1):21–25.
3. Perälä J, Suvisaari J, Saarni SI, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry*. 2007;64(1):19–28.
4. Nasrallah HA, Goldberg JF, Correll CU; SAD Working Group. Differential diagnosis and therapeutic management of schizoaffective disorder. *Ann Clin Psychiatry*. 2010;22(suppl 1):S1–S12.
5. Canuso CM, Schooler N, Carothers J, et al. Paliperidone extended-release in schizoaffective disorder: a randomized, controlled study comparing a flexible dose with placebo in patients treated with and without antidepressants and/or mood stabilizers. *J Clin Psychopharmacol*. 2010;30(5):487–495.
6. Canuso CM, Lindenmayer JP, Kosik-Gonzalez C, et al. A randomized, double-blind, placebo-controlled study of 2 dose ranges of paliperidone extended-release in the treatment of subjects with schizoaffective disorder. *J Clin Psychiatry*. 2010;71(5):587–598.
7. Canuso CM, Turkoz I, Fu DJ, et al. Role of paliperidone extended-release in treatment of schizoaffective disorder. *Neuropsychiatr Dis Treat*. 2010;6:667–679.
8. Marneros A, Deister A, Rohde A. Psychopathological and social status of patients with affective, schizophrenic and schizoaffective disorders after long-term course. *Acta Psychiatr Scand*. 1990;82(5):352–358.
9. Cheniaux E, Landeira-Fernandez J, Lessa Telles L, et al. Does schizoaffective disorder really exist? a systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood disorders. *J Affect Disord*. 2008;106(3):209–217.
10. Murru A, Pacchiarotti I, Nivoli AM, et al. What we know and what we don't know about the treatment of schizoaffective disorder. *Eur Neuropsychopharmacol*. 2011;21(9):680–690.
11. Keck PE Jr, McElroy SL, Strakowski SM. Schizoaffective disorder: role of atypical antipsychotics. *Schizophr Res*. 1999;35(suppl):S5–S12.
12. McElroy SL, Keck PE Jr, Strakowski SM. An overview of the treatment of schizoaffective disorder. *J Clin Psychiatry*. 1999;60(suppl 5):16–21, discussion 22.
13. Flynn J, Grieger TA, Benedek DM. Pharmacologic treatment of hospitalized patients with schizoaffective disorder. *Psychiatr Serv*. 2002;53(1):94–96.
14. Lerner V, Libov I, Kotler M, et al. Combination of "atypical" antipsychotic medication in the management of treatment-resistant schizophrenia and schizoaffective disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28(1):89–98.
15. Invega (paliperidone) extended-release tablets [package insert]. Titusville, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc; 2007, 2011.
16. Dolder CR, Lacro JP, Dunn LB, et al. Antipsychotic medication adherence: is

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

there a difference between typical and atypical agents? *Am J Psychiatry*. 2002;159(1):103–108.
17. Murru A, Pacchiarotti I, Nivoli AM, et al. Rates and clinical correlates of treatment non-adherence in schizoaffective bipolar patients. *Acta Psychiatr Scand*. 2012;125(5):412–418.
18. Murru A, Pacchiarotti I, Amann BL, et al. Treatment adherence in bipolar I and schizoaffective disorder, bipolar type. *J Affect Disord*. 2013;151(3):1003–1008.
19. Perkins DO, Johnson JL, Hamer RM, et al; HGDH Research Group. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. *Schizophr Res*. 2006;83(1):53–63.
20. Lindenmayer JP, Liu-Seifert H, Kulkarni PM, et al. Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. *J Clin Psychiatry*. 2009;70(7):990–996.
21. Bodén R, Brandt L, Kieler H, et al. Early non-adherence to medication and other risk factors for rehospitalization in schizophrenia and schizoaffective disorder. *Schizophr Res*. 2011;133(1–3):36–41.
22. Karve S, Markowitz M, Fu DJ, et al. Assessing medication adherence and healthcare utilization and cost patterns among hospital-discharged patients with schizoaffective disorder. *Appl Health Econ Health Policy*. 2014;12(3):335–346.
23. Pandina GJ, Lindenmayer JP, Lull J, et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. *J Clin Psychopharmacol*. 2010;30(3):235–244.
24. Pandina G, Lane R, Gopal S, et al. A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(1):218–226.
25. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
26. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
27. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278–296.
28. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Press Inc; 1996.
29. Morosini PL, Magliano L, Brambilla L, et al. Development, reliability and acceptability of a new version of the *DSM-IV* Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand*. 2000;101(4):323–329.
30. Nasrallah H, Morosini P, Gagnon DD. Reliability, validity and ability to detect change of the Personal and Social Performance scale in patients with stable schizophrenia. *Psychiatry Res*. 2008;161(2):213–224.
31. Allen MH, Daniel DG, Revicki DA, et al. Development and psychometric evaluation of a clinical global impression for schizoaffective disorder scale. *Innov Clin Neurosci*. 2012;9(1):15–24.
32. Canuso CM, Grinspan A, Kalali A, et al. Medication satisfaction in schizophrenia: a blinded-initiation study of paliperidone extended release in patients suboptimally responsive to risperidone. *Int Clin Psychopharmacol*. 2010;25(3):155–164.
33. Allison PD. *Survival Analysis Using SAS: A Practical Guide*. Cary, NC: SAS Institute; 1995.
34. Hough D, Gopal S, Vijapurkar U, et al. 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.

See supplementary material for this article at PSYCHIATRIST.COM.

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY OR COMMERCIAL PURPOSES.

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

Author(s): Dong-Jing Fu, MD, PhD; Ibrahim Turkoz, PhD; R. Bruce Simonson, BS; David P. Walling, PhD; Nina R. Schooler, PhD; Jean-Pierre Lindenmayer, MD; Carla M. Canuso, MD; and Larry Alphs, MD, PhD

DOI Number: 10.4088/JCP.14m09416

List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

© Copyright 2014 Physicians Postgraduate Press, Inc.

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

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

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

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

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

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.

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

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

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

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.

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

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.

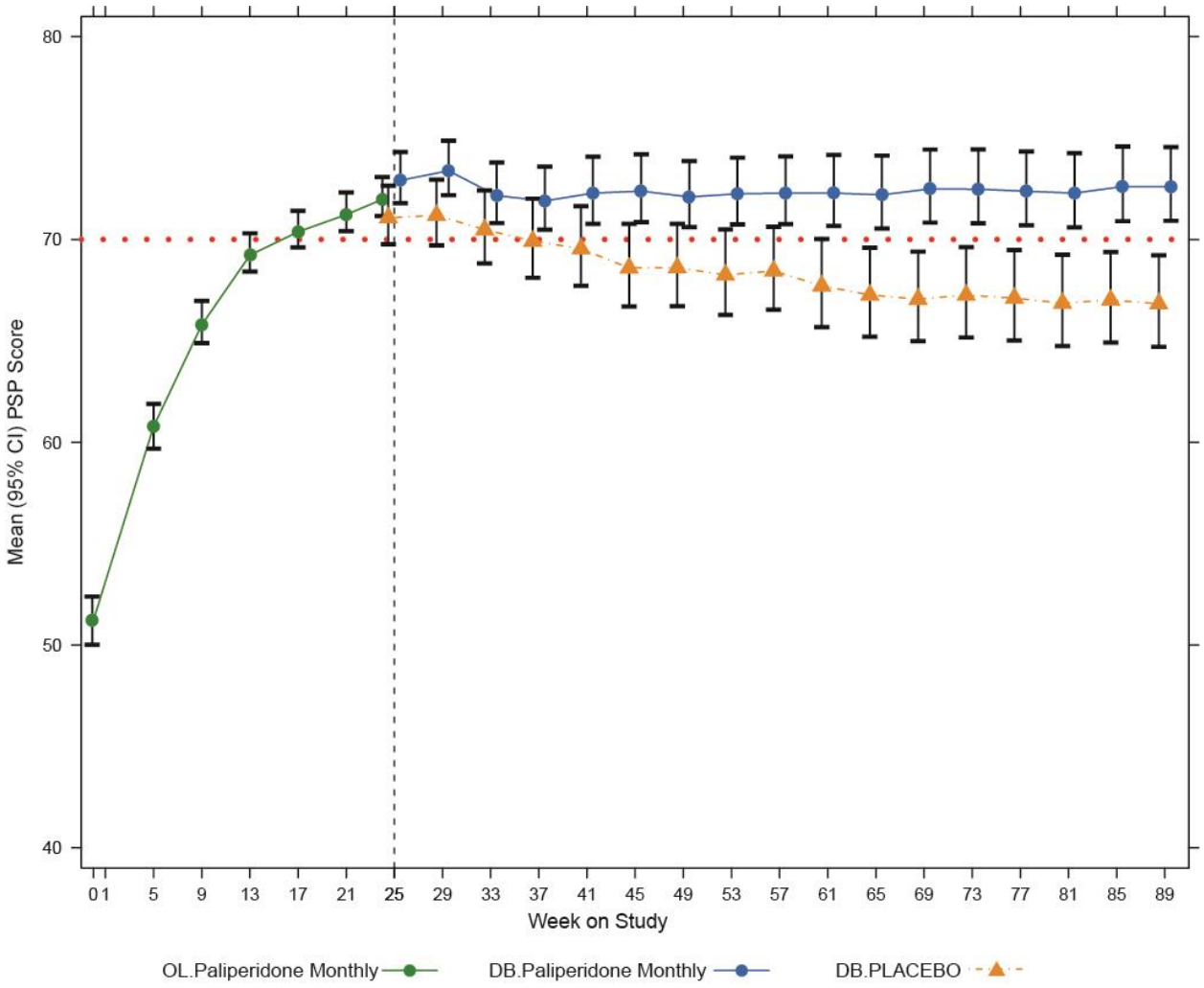
Supplementary eFigure 3. Categorical Changes in CGI-S-SCA (A) and MSQ Scores (B)

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

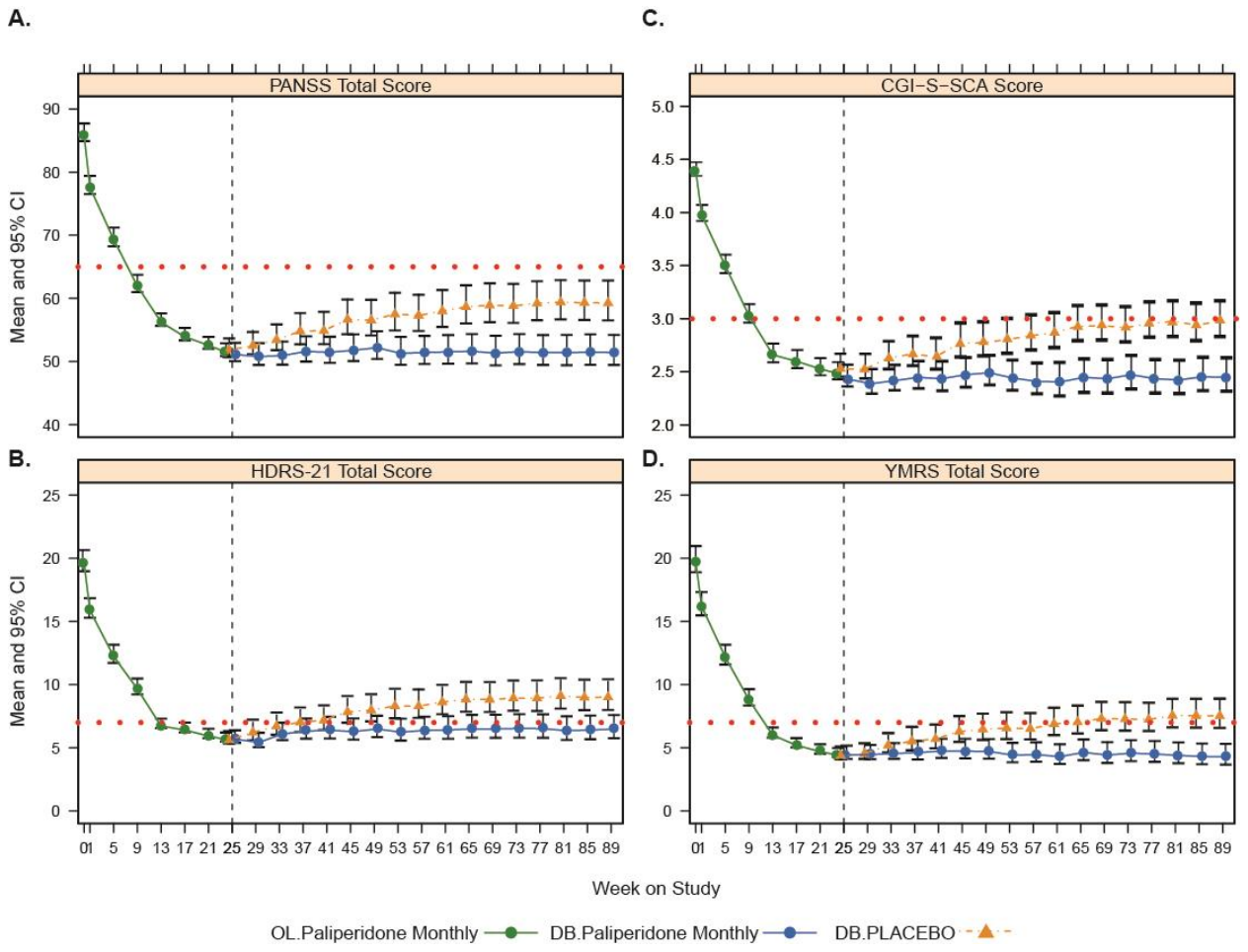
© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

Supplemental efigure 1



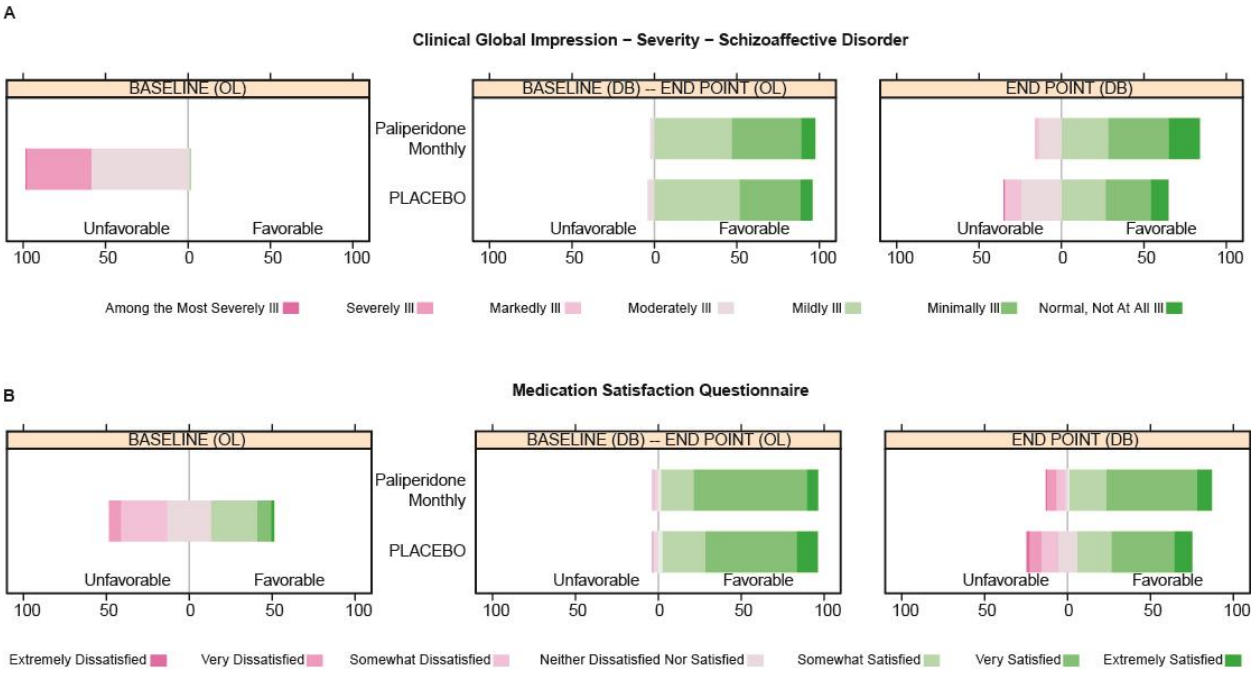
© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

Supplemental efigure 2



© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

Supplemental efigure 3



© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

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)

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

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.

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

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.

© 2014 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.