Original Investigation

Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia
A Randomized Clinical Trial

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IMPORTANCE Treatment nonadherence and relapse are common problems in patients with schizophrenia. The long-acting 3-month formulation of paliperidone palmitate, owing to its extended elimination half-life, may offer a valuable therapeutic option for these patients.

OBJECTIVE To evaluate the efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo in delaying time to relapse of schizophrenia symptoms.

DESIGN, SETTING, AND PARTICIPANTS This randomized, multicenter trial conducted from April 26, 2012, through April 9, 2014, in 8 countries consisted of 4 phases: 3-week screening phase, flexible-dose 17-week open-label transition phase, 12-week open-label maintenance phase, and open-ended double-blind (DB) phase. Of the 506 patients enrolled (aged 18-70 years; *DSM-IV-TR* diagnosis of schizophrenia), 305 were randomized to 3-month paliperidone palmitate (n = 160) or placebo (n = 145) in the DB phase.

INTERVENTIONS Patients received once-monthly doses of the 1-month formulation of paliperidone palmitate (50, 75, 100, or 150 mg eq) during the transition phase, followed by a single dose of the 3-month formulation (3.5 times the stabilized dose of once-monthly paliperidone palmitate) during the maintenance phase. Stabilized patients were randomized to receive either a fixed dose of 3-month paliperidone palmitate (175, 263, 350, or 525 mg eq) or placebo once every 3 months during the DB phase.

MAIN OUTCOMES AND MEASURES Time from randomization to the first relapse event (time to relapse) in the DB phase.

RESULTS In the interim analysis, time to first relapse was significantly different in favor of the paliperidone palmitate group vs the placebo group (hazard ratio = 3.45; 95% CI, 1.73-6.88; $P < .001$); median time to relapse was 274 days for placebo but not estimable for 3-month paliperidone palmitate. An independent data monitoring committee recommended early study termination due to efficacy. In the DB phase, 183 of 305 patients (62% with 3-month paliperidone palmitate; 58% with placebo) had at least 1 treatment-emergent adverse event; those noted more frequently in the group receiving paliperidone palmitate than in the placebo group were headache (9% vs 4%), weight increased (9% vs 3%), nasopharyngitis (6% vs 1%), and akathisia (4% vs 1%).

CONCLUSIONS AND RELEVANCE Compared with placebo, the 3-month formulation of paliperidone palmitate administered 4 times yearly significantly delayed time to relapse in patients with schizophrenia. The 3-month formulation was generally tolerable and has a safety profile consistent with other marketed paliperidone formulations.

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Relapse of schizophrenia symptoms, which can result from poor adherence to otherwise effective antipsychotic therapy, may lead to treatment resistance, cognitive impairment, personal distress, and interference with rehabilitation efforts.[1,2] Each episode of worsening symptoms presents with a risk of hospitalization, imposing significant burden on health care resources.[3-6] Patients with schizophrenia commonly lack insight into their disease and the importance of medication, compromising treatment adherence and increasing relapse frequency. Long-acting injectable (LAI) antipsychotics eliminate the need for daily dosing, thus circumventing the problem of nonadherence with antipsychotic medications and reducing the risk of relapse and hospitalization due to nonadherence among patients with schizophrenia.[7,8]

Paliperidone palmitate was originally formulated as a once-monthly atypical antipsychotic LAI and is approved for treatment of schizophrenia in adults in numerous countries.[9-11] The acute and sustained efficacy and tolerability profile of once-monthly paliperidone palmitate has been shown in more than 3800 patients.[11-22] Continued treatment with once-monthly paliperidone palmitate in patients who initially responded to it for acute worsening of symptoms resulted in a nearly 4-fold reduction in relapse risk compared with patients randomized to placebo.[16] A recently developed 3-month formulation offers a substantially longer dosing interval: injections are administered once every 3 months. This extended dosing interval offers the prospect of fewer opportunities for nonadherence than currently available LAI formulations, thus reducing relapse risk as a result of subtherapeutic plasma concentrations and its associated negative consequences in patients with schizophrenia.[2,23,24]

This double-blind (DB), placebo-controlled, relapse prevention study was designed to evaluate the efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo in delaying time to relapse of schizophrenia symptoms in patients previously treated with once-monthly paliperidone palmitate for at least 4 months.

Methods

Patients

Patients (men and women aged 18-70 years, inclusive) diagnosed with schizophrenia (by *DSM-IV-TR* criteria) for at least 1 year before screening and a Positive and Negative Syndrome Scale (PANSS) total score lower than 120 at screening and baseline were enrolled (**Figure 1**). Patients symptomatically stable on other LAI antipsychotic treatments were eligible. A stable place of residence for the previous 3 months before screening was mandatory. During initiation of the study and at subsequent times, the investigators were instructed to seek authorization from medical monitors if they elected to keep individual patients in the hospital for longer than 10 consecutive days after enrollment in the study. The medical monitors ensured that patients did not remain in the hospital, if clinically stable, beyond the second injection of once-monthly paliperidone palmitate on day 8 of the open-label (OL) transition phase. Patients were not to enter the OL maintenance phase and receive an injection of the 3-month formulation of paliperidone palmitate if still hospitalized at that time, ie, for a total of 17 weeks of OL treatment with once-monthly paliperidone palmitate, regardless of their clinical presentation. Patients were allowed assistance from an identified support person to ensure compliance with study treatment and procedures, including alerting trial staff to any signs of impending relapse. Major exclusion criteria were the following: primary, active *DSM-IV* diagnosis other than schizophrenia; significant risk of suicidal behavior; history of substance dependence within 6 months before screening; involuntary status in a psychiatric hospital at screening; or history of neuroleptic malignant syndrome, tardive dyskinesia, or any malignant neoplasm in the previous 5 years except basal cell carcinoma.

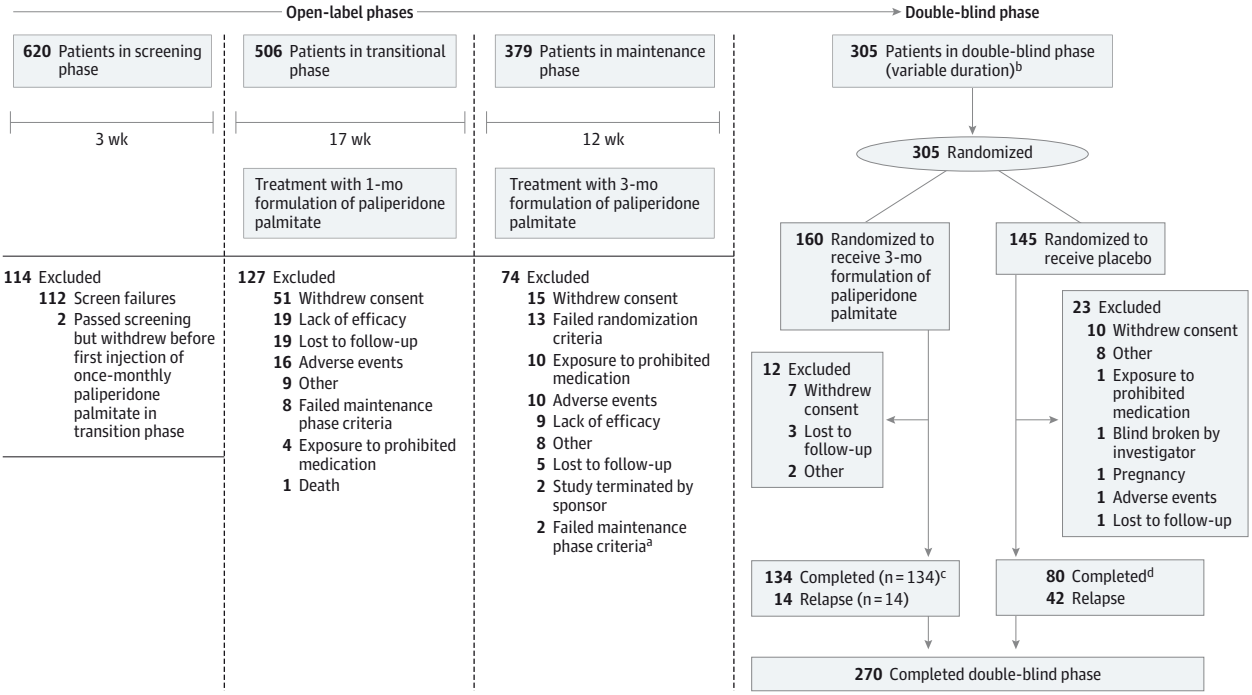
The study protocol and amendments were approved by an independent ethics committee or institutional review board, as appropriate, for each site. All studies were conducted in compliance with the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. Written informed consent was obtained from all patients before enrollment. The trial protocol is available in Supplement 1.

Study Design, Randomization, and Blinding

This randomized, DB, placebo-controlled study conducted from April 26, 2012, through April 9, 2014, included patients from 64 centers in 8 countries (Ukraine [36%], United States [31%], Romania [8%], Colombia [8%], Malaysia [6%], Mexico [6%], Turkey [3%], and South Korea [2%]). Investigators from all centers participated in the study (eAppendix 1 in Supplement 2). The study consisted of 4 phases: screening and oral tolerability testing phase (≤3 weeks), OL transition phase, OL maintenance phase, and DB phase. In the 17-week transition phase, all patients except those switching from other LAI antipsychotics or those who were receiving once-monthly paliperidone palmitate before study entry received once-monthly paliperidone palmitate for 120 days, with the following doses: day 1: 150 mg eq (deltoid); day 8: 100 mg eq (deltoid); days 36 and 64: 50, 75, 100, or 150 mg eq flexible doses (deltoid or gluteal); and day 92: same dose of once-monthly paliperidone palmitate as on day 64. At the start of the 12-week maintenance phase, patients received a single dose of 3-month paliperidone palmitate in either the deltoid or gluteal muscle (dose of 3-month paliperidone palmitate was 3.5-fold that of the final once-monthly paliperidone palmitate dose administered on day 92).

Stabilized patients were then randomized (1:1 ratio; via a sponsor-prepared computer-generated randomization scheme; administered by an interactive voice/web response system) to receive either 3-month paliperidone palmitate or placebo in a DB phase with variable length (fixed dose of 3-month paliperidone palmitate). The doses of 3-month paliperidone palmitate were 175, 263, 350, or 525 mg eq. Patients assigned to 3-month paliperidone palmitate in the DB phase received the same dose that was administered on day 120 of the maintenance phase; this dose remained fixed throughout the DB phase (eTable 1 in Supplement 2). Randomization was balanced using permuted blocks across the 2 treatment groups and stratified by study center to ensure balance of treatment allocation within a center. To maintain blinding during the DB phase, paliperi-

Figure 1. CONSORT Flow Diagram of Study Design



[a] Two patients failed to meet criteria to enter the maintenance phase but continued into the maintenance phase by mistake and received an injection of the 3-month formulation of paliperidone palmitate at visit 8. These 2 patients withdrew from the maintenance phase because they did not meet criteria to enter the maintenance phase.

[b] Duration of the double-blind phase was variable, with the patients continuing until they experienced a relapse event and completed all end-of-study assessments; met 1 or more of the study discontinuation or withdrawal criteria; or had remained relapse free during the double-blind phase until the study was terminated for efficacy at the interim analysis (occurrence of 42 relapse events) or because of 70 relapse events being recorded.

[c] The duration of exposure to the 3-month formulation of paliperidone palmitate (maintenance and double-blind phases) ranged from 16 to 540 days; the median treatment duration in the double-blind phase was 169 days.

[d] The median duration of receiving placebo in the double-blind phase was 146 days.

done palmitate and placebo were wrapped so the content was not visible and were administered by a single person distinct from other study personnel at the investigational site. The patient was not allowed to view the syringe. The placebo (Intralipid, 20%) had a similar appearance to the 1-month and 3-month formulations of paliperidone palmitate. The study drug administrator was appropriately medically trained to administer an intramuscular medication and was the only person responsible for drug accountability, receiving interactive voice/web response system information and medication allocation. Patients remained in the DB phase until they relapsed, they withdrew from the study, or the study was terminated.

Doses of paliperidone palmitate can be expressed both in terms of milligram equivalent of the pharmacologically active fraction, paliperidone, and in milligrams of paliperidone palmitate. Thus, the doses expressed as 25, 50, 75, 100, and 150 mg eq of once-monthly paliperidone palmitate equate to 39, 78, 117, 156, and 234 mg, respectively, of once-monthly paliperidone palmitate. Similarly, 175, 263, 350, and 525 mg eq of 3-month paliperidone palmitate correspond to 273, 410, 546, and 819 mg of 3-month paliperidone palmitate (eTable 2 in Supplement 2).

An independent data monitoring committee performed ongoing safety monitoring and 1 efficacy interim analysis and provided recommendations about modifying, stopping, or continuing the study. The independent data monitoring committee consisted of 4 academic psychiatrists and 1 statistician who independently reviewed safety data on a periodic (quarterly) basis and performed 1 planned unblinded efficacy analysis. The protocol planned for an interim analysis after 42 relapse events and full analysis after 70 relapse events had occurred if the study was not terminated at the interim efficacy analysis. On recommendation to terminate the study based on interim results, all ongoing patients were brought in for end-of-study evaluation. Results through the end of the DB phase after early termination of the study (ie, cumulative data including those from before the interim cutoff date) are reported herein as the final analysis, which confirmed the results of the interim analysis.

Efficacy Assessments

The primary efficacy variable was time from randomization to the first relapse event in the DB phase. Relapse was based on the definition by Csernansky et al[25] and defined as at least 1 of the following: (1) hospitalization for schizophrenia symptoms (involuntary or voluntary admission); (2) 25% increase in PANSS total

score from randomization for 2 consecutive assessments between 3 and 7 days apart for patients scoring higher than 40 at randomization or a 10-point increase for patients scoring 40 or lower at randomization; (3) increase in distinct PANSS item scores (P1 [delusions], P2 [conceptual disorganization], P3 [hallucinatory behavior], P6 [suspiciousness/persecution], P7 [hostility], or G8 [uncooperativeness]) for 2 consecutive assessments between 3 and 7 days apart; (4) clinically significant deliberate self-injury or violent behavior resulting in suicide, injury, or significant damage; or (5) suicidal or homicidal ideation and aggressive behavior. The relapse criteria were identical to those implemented in the relapse prevention studies of extended-release paliperidone[26] and once-monthly paliperidone palmitate[16] in patients with schizophrenia. Secondary efficacy end points included changes from DB baseline to end point in PANSS total, subscale, and 5-factor scores,[27] Clinical Global Impression–Severity score, and Personal and Social Performance scores.

Pharmacokinetic and Safety Assessments

The pharmacokinetic assessments are described in eAppendix 2 in Supplement 2. Safety assessments included treatment-emergent adverse events (TEAEs), extrapyramidal symptom (EPS) rating scales, clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms, physical examination findings, and injection-site evaluations.

Statistical Analysis

The sample size determination is described in eAppendix 2 in Supplement 2.

The Kaplan-Meier method was used to assess the primary efficacy variable (time to relapse), and the log-rank test (2-sided) was used to compare treatment differences. Treatment comparison between 3-month paliperidone palmitate and placebo in changes from baseline to end point of PANSS total, subscale, and 5-factor scores, Personal and Social Performance scores, and Clinical Global Impression–Severity score during the DB phase was performed using an analysis-of-covariance model with treatment and country as factors and DB baseline value as a covariate. All secondary efficacy analyses were performed at the significance level of $\alpha = .05$ (2-sided) across treatment groups with no adjustments for multiplicity. Cox proportional hazards models were constructed to individually examine the effect of covariates (age, sex, race, body mass index [BMI; calculated as weight in kilograms divided by height in meters squared], and geographic region) on the primary efficacy results. Least-squares estimates of the treatment differences and 95% confidence intervals were calculated.

The study was to be stopped if efficacy was established (at a 2-sided significance level of $\alpha = .0101$) at the preplanned interim analysis (after 42 relapse events). If the study was not terminated due to nonsignificant results, the final analysis (after 70 relapse events) was to be performed at a significance level of $\alpha = .0464$ (2-sided).

Results

Of the 506 patients enrolled, 305 (60%) were randomized to either 3-month paliperidone palmitate (n = 160) or placebo (n = 145) in the DB phase. Of 305 randomized patients, a total of 270 (89%) completed the study (Figure 1). The median treatment duration was 120 days for the transition phase, 85 days for the maintenance phase, and 169 days for the group receiving 3-month paliperidone palmitate and 146 days for the placebo group in the DB phase. Demographic and baseline characteristics were well balanced between the groups (**Table 1**). The most common reason for discontinuation from this study was consent withdrawal. A total of 11 (2%), 42 (8%), 241 (48%), and 212 (42%) of the patients received the final dose of 50, 75, 100, and 150 mg eq of once-monthly paliperidone palmitate, respectively, in the transition phase, while 9 (2%), 36 (9%), 185 (49%), and 149 (39%) of the patients received 175, 263, 350, and 525 mg eq of 3-month paliperidone palmitate, respectively, at week 17 in the maintenance phase. Of these, 6 (4%) of the patients receiving 175 mg eq, 15 (9%) receiving 263 mg eq, 78 (49%) receiving 350 mg eq, and 61 (38%) receiving 525 mg eq entered the DB phase. A greater proportion of patients who entered the DB phase receiving 525 mg eq of 3-month paliperidone palmitate (14 of 61 patients [23%]) continued in the study to DB week 36 vs other dose groups (175 mg eq: 0 of 6 patients; 350 mg eq: 8 of 78 patients [10%]; 263 mg eq: 3 of 15 patients [20%]).

Efficacy

Primary

The interim analysis (considered the primary analysis) was conducted on data collected from April 26, 2012, through data cutoff on January 24, 2014. The analysis set (DB) for the interim analysis included 283 patients (3-month paliperidone palmitate, n = 148; placebo, n = 135). The interim analysis revealed a significant difference between the 2 treatment groups for time to relapse of schizophrenia symptoms, in favor of 3-month paliperidone palmitate (hazard ratio = 3.45; 95% CI, 1.73-6.88; $P < .001$); the median time to relapse was 274 days for the placebo group but was not estimable for the group receiving 3-month paliperidone palmitate (**Figure 2**A). Based on the interim analysis, 31 patients (23%) in the placebo group and 11 patients (7%) in the group receiving 3-month paliperidone palmitate experienced a relapse event during the DB phase (eTable 3 in Supplement 2). Consequently, the independent data monitoring committee recommended early study termination for efficacy.

The final analysis set (DB) included 305 patients (3-month paliperidone palmitate: n = 160; placebo: n = 145). Final analysis results were consistent with that of interim analysis, confirming superiority of 3-month paliperidone palmitate over placebo for delaying time to relapse of schizophrenia symptoms ($P < .001$; hazard ratio = 3.81; 95% CI, 2.08-6.99); the median time to relapse was 395 days for the placebo group but was not estimable for the group receiving 3-month paliperidone palmitate (Figure 2B). A total of 42 patients (29%) in the placebo group and 14 patients (9%) in the group receiving 3-month paliperidone palmitate experienced a relapse event during the DB phase (eTable 3 in Supplement 2). Additionally, based on Cox proportional hazards model, the efficacy of 3-month paliperidone palmitate with regard to time to relapse was consistent regardless of age, sex, race, BMI, or region ($P < .001$ for all, regardless of which factor is included in the model) (eTable 4 and eTable 5 in Supplement 2).

Table 1. Demographic and Baseline Characteristics in the Double-Blind Phase for the Intent-to-Treat Analysis Set

Characteristic	Placebo (n = 145)	3-mo Paliperidone Palmitate (n = 160)	Total (n = 305)
Age, mean (SD), y	38.5 (11.16)	37.1 (10.87)	37.8 (11.01)
Male, No. (%)	110 (76)	118 (74)	228 (75)
Race, No. (%)			
White	91 (63)	104 (65)	195 (64)
Black or African American	21 (14)	24 (15)	45 (15)
Asian	15 (10)	14 (9)	29 (10)
Other	18 (12)	17 (11)	35 (11)
Multiple	0	1 (1)	1 (<1)
Weight, mean (SD), kg	77.1 (15.53)	78.1 (14.97)	77.6 (15.22)
BMI, mean (SD)	26.2 (4.57)	26.2 (4.51)	26.2 (4.53)
Age at schizophrenia diagnosis, mean (SD), y	27.7 (8.98)	26.3 (8.24)	26.9 (8.61)
Use of depot antipsychotics prior to study start, No. (%)			
Yes	25 (17)	28 (18)	53 (17)
No	120 (83)	132 (83)	252 (83)
No. of prior hospitalizations, No. (%)[a]	128	146	274
0	51 (40)	48 (33)	99 (36)
1	44 (34)	48 (33)	92 (34)
2	18 (14)	25 (17)	43 (16)
3	7 (5)	14 (10)	21 (8)
≥4	8 (6)	11 (8)	19 (7)
Score at double-blind phase baseline, mean (SD)[b]			
PANSS	54.2 (9.34)	54.9 (9.95)	54.5 (9.66)
CGI-S	2.8 (0.65)	2.7 (0.67)	2.7 (0.66)
PSP	68.6 (9.01)	68.8 (9.27)	68.7 (9.14)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CGI-S, Clinical Global Impression–Severity; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance.

[a] Number of prior hospitalizations for psychosis within 24 months before study start.

[b] Scores on the PANSS range from 30 to 210, with higher scores indicating more symptoms; CGI-S scores range from 1 to 7, with higher scores indicating a more severe overall clinical condition; and PSP scores range from 1 to 100, with higher scores indicating better functioning.

Secondary

The mean (SD) PANSS total score at DB baseline was 54.9 (9.95) for patients randomized to 3-month paliperidone palmitate and 54.2 (9.34) for those randomized to placebo. The mean PANSS total score remained stable during the DB phase for patients receiving 3-month paliperidone palmitate but increased in the placebo group, with a significant difference in change from the DB baseline (mean [SD] change, −0.5 [8.36] vs 6.7 [14.40], respectively; $P < .001$; least-squares means difference, −7.2; 95% CI, −9.87 to −4.60) (**Figure 3**). There were also significant differences ($P \leq .005$) in mean change from DB baseline to end point between the group receiving 3-month paliperidone palmitate and the placebo group for PANSS subscale and Marder factor scores (except negative subscale and negative symptoms factor), Clinical Global Impression-Severity score (mean [SD] change, 0.1 [0.60] vs 0.4 [0.87], respectively; $P < .001$; least-squares means difference, −0.3; 95% CI, −0.50 to −0.18), and Personal and Social Performance scores (mean [SD] change, −0.5 [6.63] vs −4.2 [9.70], respectively; $P < .001$; least-squares means difference, 3.8; 95% CI, 1.89 to 5.65) (eTable 6 and eTable 7 in Supplement 2). Change in remitter status (eTable 8 in Supplement 2) supports maintenance of efficacy in the DB phase for those continuing treatment with 3-month paliperidone palmitate compared with those randomized to placebo.

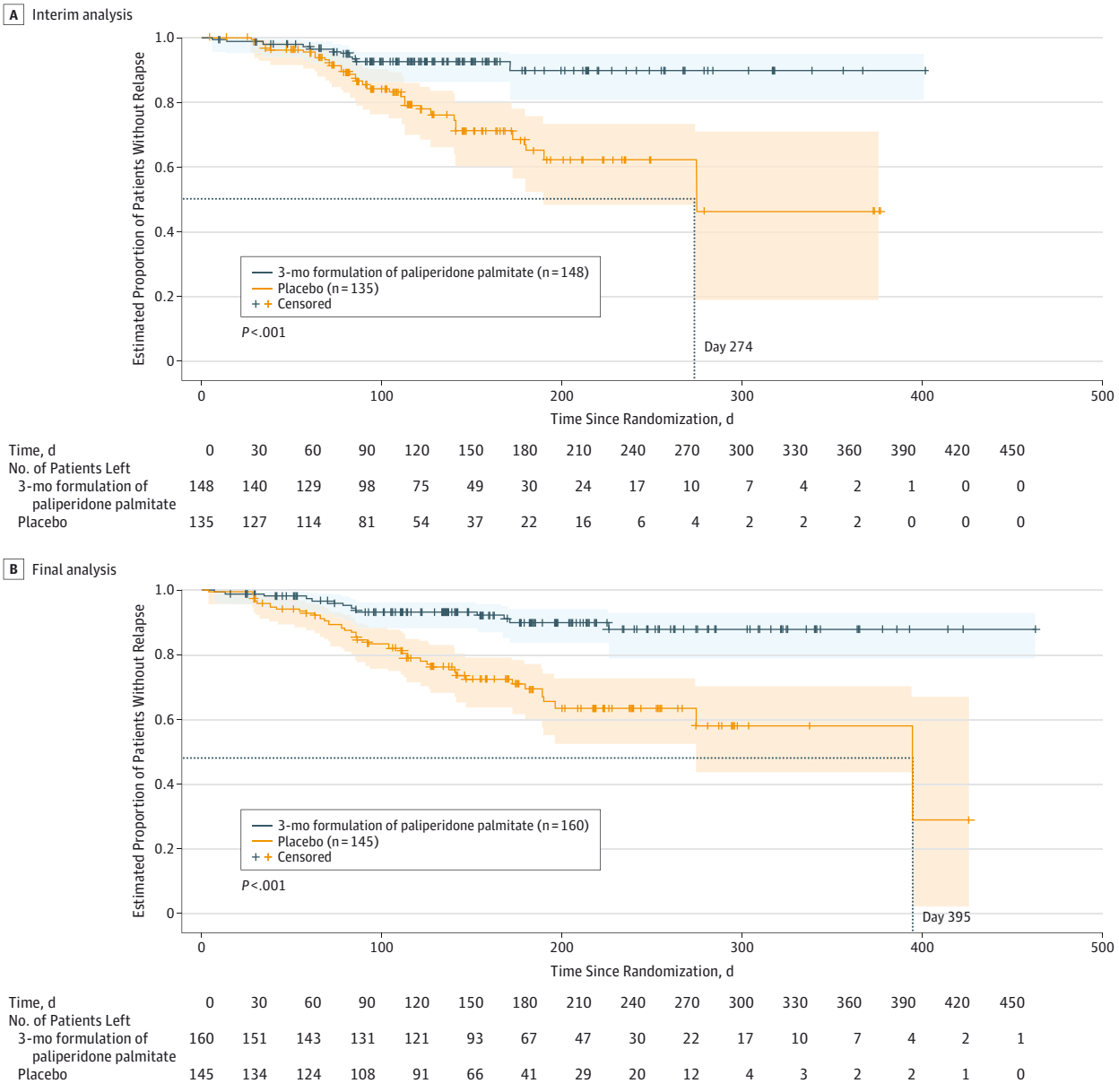
Pharmacokinetics and Safety

The results for pharmacokinetics are described in eAppendix 3 and the eFigure in Supplement 2.

Regarding safety, a total of 330 of 506 patients (65%) in the OL phase and 183 of 305 patients (60%) in the DB phase (62% of those receiving 3-month paliperidone palmitate vs 58% of those receiving placebo) had at least 1 TEAE. The most frequently reported TEAEs (≥2%) in the group receiving 3-month paliperidone palmitate during the maintenance phase were anxiety (6%), insomnia (5%), weight increased (4%), and headache (3%) (eTable 9 in Supplement 2). During the maintenance phase, the TEAEs that led to study discontinuation in more than 1 patient included psychiatric disorders (3 [1%]) and schizophrenia (2 [0.5%]). The most commonly occurring EPS-related TEAEs (≥1%) were those grouped under hyperkinesia (6 [2%]) and parkinsonism (5 [1%]). One patient (0.3%) experienced a hyperglycemia-related TEAE of type 2 diabetes mellitus during the maintenance phase.

During the DB phase, the most common TEAEs occurring more frequently in the group receiving 3-month paliperidone palmitate than in the placebo group were headache (9% vs 4%, respectively), weight increased (9% vs 3%, respectively), nasopharyngitis (6% vs 1%, respectively), and EPS-related TEAEs (8% vs 3%, respectively [akathisia, 4% vs 1%, respectively]). The placebo group compared with the group receiving

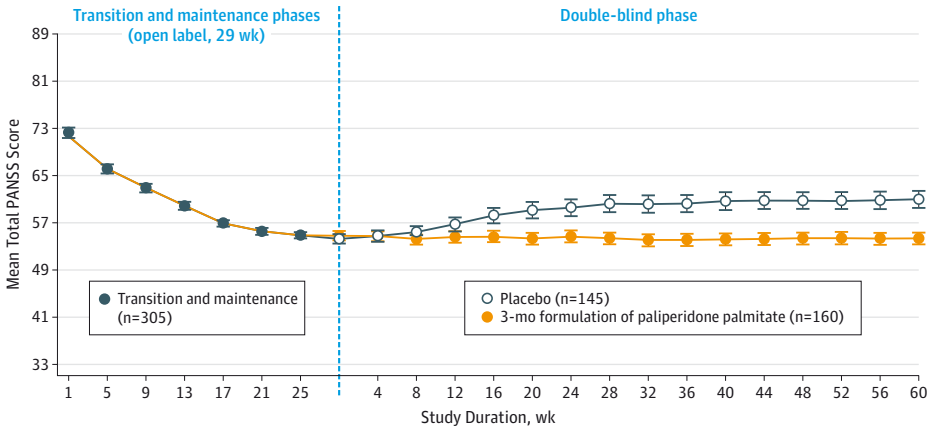
Figure 2. Kaplan-Meier Plot of Time to Relapse During the Double-Blind Phase



The median time to relapse indicates the time (in days) since randomization at which the cumulative survival function equals 0.5. Shaded areas indicate 95% confidence interval for the estimated proportion of patients who remained in the study without relapse at distinct times after randomization in the double-blind phase. A, Interim analysis. The median time to relapse was 274 days for placebo and was not estimable for the 3-month formulation of paliperidone palmitate. B, Final analysis. The median time to relapse was 395 days for placebo and was not estimable for 3-month paliperidone palmitate. Of the 160 patients randomized to 3-month paliperidone palmitate in the double-blind phase (175 mg eq: 6 patients [4%]; 263 mg eq: 15 patients [9%]; 350 mg eq: 78 patients [49%]; and 525 mg eq: 61 patients [38%]), a total of 25 patients (16%) continued at week 36. A greater proportion of patients receiving 525 mg eq of 3-month paliperidone palmitate (14 of 61 patients [23%]) continued in the study to double-blind phase week 36 vs other dose groups (175 mg eq: 0 of 6 patients; 350 mg eq: 8 of 78 patients [10%]; 263 mg eq: 3 of 15 patients [20%]).

3-month paliperidone palmitate more commonly had anxiety (11% vs 8%, respectively), insomnia (12% vs 7%, respectively), and weight decreased (8% vs 1%, respectively) (**Table 2**). A higher percentage of patients who received placebo (8 of 145 [6%]) vs those treated with 3-month paliperidone palmitate (4 of 160 [3%]) experienced glucose-related TEAEs. One of 145 patients (1%) in the placebo group and 15 of 160 patients (10%) in the group receiving 3-month paliperidone palmitate experienced a clinically significant increase in body weight (≥7%) from DB baseline to end point. Six patients (4%) in the group receiving 3-month paliperidone palmitate reported injection site-related TEAEs, of which injection site pain was most frequently reported (2 patients [1%]). Prolactin-related TEAEs (amenorrhea) occurred in 1 of 42 women (2%) in the group

Figure 3. Positive and Negative Syndrome Scale (PANSS) Total Scores Over Time



Error bars indicate standard error.

treated with 3-month paliperidone palmitate. A higher percentage of patients who received placebo than those treated with 3-month paliperidone palmitate experienced a treatment-emergent abnormally high heart rate relative to the predose average (10 of 141 [7%] vs 3 of 155 [2%], respectively). Serious TEAEs occurred 4 times more often in the placebo group than in the group receiving 3-month paliperidone palmitate (10% vs 3%, respectively) and were mostly related to increase in psychiatric symptoms. Only 1 TEAE (increased transaminase levels, in the placebo group) led to treatment discontinuation during the DB phase. No deaths were reported during the DB phase; 1 death (in a patient treated with once-monthly paliperidone palmitate) was reported during the OL phase due to a TEAE of megacolon, which was considered not related to the study agent by the investigator. Additional details are included in eTables 9 to 16 in Supplement 2.

Discussion

Relapse episodes culminating in diminished functioning, homelessness, incarceration, and increased societal costs[3-5] are common downstream outcomes of poor adherence to potentially effective antipsychotic therapy in patients with schizophrenia.[2,6,24] In the United States, fewer than 50% of Medicaid patients with schizophrenia were reported to be adherent with their prescribed antipsychotic regimen between 1998 and 2000.[28] Use of LAIs has resulted in increased treatment adherence, delaying symptom relapse and reducing the risk of rehospitalization in patients with schizophrenia.[7,8,16,29,30] This novel formulation of paliperidone palmitate with a reduced dosing frequency of 1 injection every 3 months could further mitigate the low treatment adherence in schizophrenia and improve patients' and caregivers' quality of life. The reduced dosing frequency is likely to be of particular benefit to patients with limited access to health care, eg, those who live in an underserved rural or inner city setting and have difficulties coordinating biweekly or once-monthly transportation for injection visits. When nonadherence is identified in these patients, there is a wider window than with other available antipsychotic formulations within which they can be encouraged to become adherent before plasma concentrations decrease below therapeutic thresholds.

In this study, the 3-month formulation of paliperidone palmitate significantly delayed time to relapse of schizophrenia symptoms vs placebo. Patients randomly assigned to placebo were nearly 4 times more likely to relapse during the DB phase than those who continued to receive 3-month paliperidone palmitate. Even though comparisons across studies with similar design can be confounded for multiple reasons, the estimated median time to relapse for patients switched to placebo after stabilization on various formulations of paliperidone show that 3-month paliperidone palmitate has a longer time to relapse compared with the estimates with once-monthly paliperidone palmitate and oral extended-release paliperidone (395 vs 172 and 58 days, respectively).[16,26] Patients at risk for sudden discontinuation from treatment could therefore benefit from 3-month paliperidone palmitate, providing protection from relapse for up to 1 year after the last dose.

The secondary end point results corroborated the primary efficacy findings. The use of a randomized withdrawal design mimics sudden discontinuation of treatment, which commonly occurs under typical clinical conditions in patients with schizophrenia. A recent survey found that among patients with schizophrenia who admit noncompliance, more than half reported stopping antipsychotic treatment without clinician knowledge or support.[31]

The results of this study were consistent with the efficacy and safety of once-monthly paliperidone palmitate in maintaining symptomatic control in a comparable relapse prevention study in patients with schizophrenia.[16] Within this study, the efficacy of 3-month paliperidone palmitate with regard to time to relapse was consistent across all subgroups assessed (age, sex, race, BMI, and geographic region). Patients enrolled in the study were first treated for 4 months with once-monthly paliperidone palmitate to establish safety and efficacy of paliperidone released from once-monthly paliperidone palmitate and to optimize the dose before the first injection of 3-month paliperidone palmitate. This study was not designed to assess the efficacy or safety of distinct doses

of 3-month paliperidone palmitate; however, it is noteworthy that a greater proportion of patients who were maintained on 525 mg eq than on 350 mg eq remained in the DB phase beyond 36 weeks.

The 3-month formulation of paliperidone palmitate has an extended apparent elimination half-life that permits dosing once every 3 months (Paulien Ravenstijn, PhD, B.R., A. Savitz, Mahesh N. Samtani, PhD, I.N., Cheng-Tao Chang, PhD, Marc De Meulder, MSc, D.W.H., and S.G., unpublished data, February 29, 2008, to May 14, 2014), offering a potential new treatment option in schizophrenia. Steady-state paliperidone plasma concentrations during the maintenance and DB phases were consistent with the observed steady-state exposure for corresponding doses of once-monthly paliperidone palmitate.[10,12] However, the number of plasma samples collected was limited, especially in the later part of the DB phase.

The dose of 3-month paliperidone palmitate determined by the prior dose of once-monthly paliperidone palmitate and a 3.5-fold dose conversion ratio was generally tolerable; safety findings of 3-month paliperidone palmitate observed during the 12-week maintenance phase and the subsequent DB phase of variable duration were consistent with those observed in other clinical trials with paliperidone palmitate,[17,18,20,22] and no new safety signals were detected. The occurrences of EPS-related TEAEs in the DB phase were generally similar to those reported in previous studies of once-monthly paliperidone palmitate.[16,17,20,22] Akathisia occurred more frequently with 3-month paliperidone palmitate relative to placebo in this study (4% vs 1%, respectively) than in a previous, similarly designed study (0.5% for once-monthly paliperidone palmitate vs none for placebo; D.W.H., S.G., Ujjwala Vijapurkar, PhD, Marissa Bernstein, PhD, and Anna Mendlin, PhD, unpublished data, March 4, 2005, through February 20, 2007). The mean body weight increase from OL baseline to DB end point observed for the group receiving 3-month paliperidone palmitate compared with the placebo group in this study (2.38 vs 0.55 kg, respectively) was consistent with that in the similarly designed study of once-monthly paliperidone palmitate (1.9 vs 0.0 kg, respectively).[17] However, the proportion of patients with an abnormal increase in body weight (≥7%) from DB baseline to end point in the group receiving 3-month paliperidone palmitate compared with the placebo group (10% vs 1%, respectively) was relatively higher than the proportion of patients in the once-monthly paliperidone palmitate group with the same body weight increase, in the similarly designed study of once-monthly paliperidone palmitate compared with placebo (6% vs 3%, respectively).[17] The difference in duration of follow-up during the DB phase between the 2 studies could be a possible confound in the interpretation of population mean or individual patient data for changes in body weight. Consistent with the known pharmacology of paliperidone, mean prolactin levels increased with treatment with 3-month paliperidone palmitate, more so in women than men; however, there were very few corresponding reports of potentially prolactin-related TEAEs.

While interpreting these results, certain limitations should be considered. As patients with a recent history of substance dependence were excluded from enrollment in this study, data may not be directly generalizable to this important patient subgroup that is particularly vulnerable to relapse with alternate, shorter-acting formulations of atypical antipsychotics. The relapse prevention design was based on the principle of enrichment; clinical stability was required before entry into maintenance and DB phases. Hence, results of the DB analysis set may not reflect the true efficacy of 3-month paliperidone palmitate for relapse prevention in all patients with schizophrenia irrespective of their initial response to once-monthly paliperidone palmitate as monotherapy in the treatment of acute worsening of symptoms. The safety profiles of the 1-month and 3-month formulations of paliperidone palmitate within this study cannot be directly compared as the

Table 2. Summary of TEAEs Reported During the Double-Blind Phase in the Safety Analysis Set[a]

Variable	No. (%)	
	Placebo (n = 145)	3-mo Paliperidone Palmitate (n = 160)
Patients with TEAEs	84 (58)	99 (62)
Possibly drug-related TEAE	27 (19)	54 (34)
TEAE leading to drug withdrawal	1 (1)	0
Patients with ≥1 serious TEAE	15 (10)	4 (3)
TEAEs reported in ≥2% of patients in either group		
Headache	6 (4)	14 (9)
Anxiety	16 (11)	13 (8)
Insomnia	17 (12)	11 (7)
Nasopharyngitis	2 (1)	9 (6)
Upper respiratory tract infection	3 (2)	6 (4)
Cough	3 (2)	5 (3)
Urinary tract infection	2 (1)	5 (3)
Influenza	3 (2)	3 (2)
Schizophrenia	15 (10)	2 (1)
Weight decreased	11 (8)	2 (1)
Agitation	3 (2)	2 (1)
Decreased appetite	3 (2)	1 (1)
Irritability	3 (2)	1 (1)
Suicidal ideation	3 (2)	0
EPS-related TEAEs	5 (3)	13 (8)
Akathisia	1 (1)	7 (4)
Diabetes mellitus– and hyperglycemia-related TEAEs	8 (6)	4 (3)
Blood glucose level increased	3 (2)	3 (2)
Hyperglycemia	4 (3)	0
Weight gain-related TEAEs	5 (3)	15 (9)
Weight increased	5 (3)	14 (9)
Injection site-related TEAEs	0	6 (4)
Prolactin-related TEAEs	0	1 (1)
Amenorrhea	0	1 (2)[b]

Abbreviations: EPS, extrapyramidal symptom; TEAEs, treatment-emergent adverse events.

[a] The TEAEs reported herein occurred during the double-blind phase; if a patient developed a TEAE during the open-label phase (either transition or maintenance) and the TEAE did not worsen during the double-blind phase, it would not be captured.

[b] Sample size was 42 women.

formulations were administered sequentially, ie, during distinct phases of the study, and once-monthly paliperidone palmitate was provided as OL treatment only. In addition, the fixed-dosing regimen implemented during the DB phase of this study prevents evaluation of the ratio of benefit to risk for distinct dose levels of 3-month paliperidone palmitate for relapse prevention. In clinical practice, dose selection of 3-month paliperidone palmitate will be informed by the dose of once-monthly paliperidone palmitate, affording an optimal ratio of benefit to risk as determined for individual patients in the period of prior treatment with once-monthly paliperidone palmitate. Because of differences in duration of follow-up and exposure in the DB phase, comparison of data for secondary efficacy and safety end points between treatment groups, as based on changes in continuous or categorical variable over time (eg, body weight, BMI), should be interpreted with caution within this study and with reference to the similarly designed study of once-monthly paliperidone palmitate. Data will be available to compare the safety profiles of the 1-month and 3-month formulations of paliperidone palmitate directly when an ongoing noninferiority study of the 2 LAI formulations of paliperidone for the treatment of patients with schizophrenia is completed (clinicaltrials.gov identifier NCT01515423).

Conclusions

Compared with placebo, the 3-month formulation of paliperidone palmitate significantly delayed time to first relapse in patients with schizophrenia previously treated with once-monthly paliperidone palmitate for at least 4 months. Furthermore, 3-month paliperidone palmitate was generally tolerable with a safety profile consistent with other marketed formulations of paliperidone. The 3-month formulation allows patients to maintain therapeutic paliperidone plasma levels with fewer injections, which could subsequently improve functional outcome and quality of life with a sufficient follow-up period. The extended dosing interval may offer particular advantages for patients and their caregivers or families who are struggling with continuous treatment or have limited health care access and are thus at increased relapse risk from treatment discontinuation.

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