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A Controlled, Evidence-Based Trial of Paliperidone Palmitate, A Long-Acting Injectable Antipsychotic, in Schizophrenia

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Paliperidone palmitate is a long-acting injectable antipsychotic agent. This 13-week, multicenter, randomized (1 : 1 : 1 : 1), double-blind, parallel-group study evaluated the efficacy, safety, and tolerability of fixed 25, 50, and 100 milligram equivalent (mg equiv.) doses of paliperidone palmitate *vs* placebo administered as gluteal injections on days 1 and 8, then every 4 weeks (days 36 and 64) in 518 adult patients with schizophrenia. The intent-to-treat analysis set ($N = 514$) was 67% men and 67% White, with a mean age of 41 years. All paliperidone palmitate dose groups showed significant improvement *vs* placebo in the Positive and Negative Syndrome Scale (PANSS) total score (primary efficacy measure; 25 and 50 mg equiv., $p = 0.02$; 100 mg equiv., $p < 0.001$), as well as Clinical Global Impression Severity scores ($p \leqslant 0.006$) and PANSS negative and positive symptom Marder factor scores ($p \leqslant 0.04$). The Personal and Social Performance scale showed no significant difference between treatment groups. The overall incidence of treatment-emergent adverse events was similar between groups. Parkinsonism, the most frequently reported extrapyramidal symptom, was reported at similar rates for placebo (5%) and paliperidone palmitate (5–6% across doses). The mean body mass index and mean weight showed relatively small dose-related increases during paliperidone palmitate treatment. Investigator-evaluated injection-site pain, swelling, redness, and induration were similar across treatment groups; scores for patient-evaluated injection-site pain (visual analog scale) were similar across groups and diminished with time. All doses of once-monthly paliperidone palmitate were efficacious and generally tolerated, both locally and systemically. Paliperidone palmitate offers the potential to improve outcomes in adults with symptomatic schizophrenia.
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Keywords: paliperidone palmitate; schizophrenia; long acting; injectable; antipsychotic; efficacy

INTRODUCTION

Atypical antipsychotics are the mainstay of therapy for patients with schizophrenia. These agents are generally viewed as having efficacy at least equivalent to that of older neuroleptics, with a lower risk for extrapyramidal symptoms (EPSs) and associated anhedonia and apathy, impaired cognition, and dysphoria (Lieberman *et al*, 2005; Tandon, 2002; Tandon and Jibson, 2002). Although considered a significant advancement over older drugs, atypical antipsychotics still have limited efficacy in many patients (Stroup *et al*, 2006), particularly with respect to negative and cognitive symptoms. Tolerability, in some patients, remains a concern (Lieberman *et al*, 2005).

Adherence to therapy is also an important challenge in the management of schizophrenia. The adverse effects of antipsychotic treatment, as well as restrictive dosing regimens (such as the requirement to take drugs with food or multiple times a day), are a few of several factors that may compromise oral antipsychotic treatment adherence (Cooper *et al*, 2007; Gianfrancesco *et al*, 2006; Keith and Kane, 2003). General dissatisfaction with oral antipsychotic therapy was underscored by results from the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study, which indicated that although 10–18% of patients discontinued initial treatment because of adverse events,

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~30% discontinued for reasons unrelated to tolerability, safety, or efficacy (Lieberman *et al*, 2005). Long-acting injectable (LAI) antipsychotics offer the potential to improve adherence, and to provide additional benefits, such as improving long-term treatment outcomes (Kane *et al*, 2003). The LAI formulation of risperidone, which was the first injectable atypical antipsychotic, was developed in response to the need for new and better-tolerated LAI antipsychotics and to decrease relapse (Taylor *et al*, 2004).

Paliperidone, the active metabolite of the atypical antipsychotic risperidone, is one of the most recent oral atypical antipsychotics to become available for the treatment of schizophrenia. As an extended-release oral formulation, it was effective and tolerated in controlled clinical trials (Davidson *et al*, 2007; Kane *et al*, 2007; Kramer *et al*, 2007; Marder *et al*, 2007). Recently, an LAI intramuscular formulation of this compound, paliperidone palmitate, became the first once-monthly atypical antipsychotic approved in the United States for schizophrenia treatment. Paliperidone palmitate has important advantages over presently available medications, including its efficacy and tolerability in both acute and maintenance treatment, dosing options in both gluteal and deltoid muscles, no need for oral supplementation, and ready-to-use syringes that do not require reconstitution or refrigeration. A phase 2 trial of two doses of paliperidone palmitate (50 and 100 milligram equivalents (mg equiv.)) suggested that it is effective and tolerated by patients with schizophrenia (Kramer *et al*, 2010). The present confirmatory phase 3 trial, designed and sponsored by Johnson & Johnson Pharmaceutical Research & Development, LLC, assessed the safety and efficacy of three fixed doses of paliperidone palmitate, injected into the gluteal muscle, in a larger sample of patients with schizophrenia.

MATERIALS AND METHODS

Paliperidone Palmitate Doses

Doses of paliperidone palmitate can be expressed either in terms of milligram equivalents of the pharmacologically active fraction, paliperidone, or in milligrams of paliperidone palmitate. Thus, the doses expressed as 'paliperidone palmitate 25, 50, and 100 mg equiv.' equate to 39, 78, and 156 mg, respectively, of paliperidone palmitate.

Study Design

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-response study was designed to evaluate the efficacy and safety of three fixed doses (25, 50, and 100 mg equiv.) of paliperidone palmitate *vs* placebo. Patients were enrolled at 38 centers in 5 countries: the United States (19 centers), South Africa (2 centers), Bulgaria, Romania, and Russia (17 centers total in these 3 European countries). The study included a screening period of up to 7 days and a 13-week double-blind treatment period. Hospitalization was required for all patients from days 1 through 8 of treatment. An Independent Ethics Committee or Institutional Review Board reviewed the study protocol. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Patients or their legal representatives provided written informed consent before participating.

Patients

Eligible patients were men or women (if not pregnant, nursing, or planning to become pregnant) who met the diagnostic criteria for schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision* (DSM-IV-TR) for at least 1 year before screening. Patients had a Positive and Negative Syndrome Scale (PANSS) total score at screening and baseline of 70–120 (inclusive) and a body mass index (BMI) $>15.0\,kg/m^2$, and were able and willing to meet or perform study requirements. Major exclusion criteria are summarized in Table 1.

Treatments

Patients were randomly assigned in a 1 : 1 : 1 : 1 ratio to receive matched placebo injections (Intralipid, 2007), or intramuscular fixed doses of paliperidone palmitate (25, 50, or 100 mg equiv.), without oral supplementation. Initial doses were administered on days 1 and 8, then every 4 weeks (days 36 and 64) of the double-blind treatment period. All doses of study medication were injected into the gluteal muscle on the left or right side in an alternating manner. Patients were followed up for 28 days after the last injection on day 64.

Patients without documented previous exposure to risperidone or paliperidone underwent an oral tolerability test (day −7 to day −1). Only patients who tolerated the oral test medication could continue into the study.

Data Analysis

The intent-to-treat (ITT) analysis set included all patients who were randomized, received $\geqslant 1$ dose of double-blind study medication, and had both the baseline and $\geqslant 1$ postbaseline efficacy assessment. The safety analysis set included all patients who were randomized and received $\geqslant 1$ dose of double-blind study medication. The primary efficacy variable was the change from baseline to end point (last observation carried forward (LOCF) approach: day 92 or the last postbaseline assessment in the double-blind period) in PANSS total score. Secondary efficacy variables were changes from baseline to end point in Clinical Global Impression-Severity (CGI-S) and Personal and Social Performance (PSP) scales (Morosini *et al*, 2000). Other efficacy variables included PANSS subscales, PANSS Marder factor scores, and treatment responder rate (defined as patients with a $\geqslant 30\%$ decrease from baseline in PANSS total score at end point).

Safety evaluations included reports of adverse events, EPS rating scales (Abnormal Involuntary Movement Scale: AIMS; Guy, W (1976)), Barnes Akathisia Rating Scale (BARS; Barnes (1989)), and Simpson Angus Scale (SAS; Simpson and Angus (1970)), clinical laboratory tests, 12-lead electrocardiograms, physical examination findings, investigators' evaluation of the injection site, and patients' evaluations of pain at the injection site.

Table 1 Exclusion Criteria

Primary active DSM-IV Axis I diagnosis other than schizophrenia
Decrease of at least 25% in the PANSS total score between screening and baseline
Unable to provide consent or involuntarily committed to psychiatric hospitalization
DSM-IV diagnosis of active substance dependence within 3 months before screening
History of treatment resistance, defined as failure to respond to two adequate trials of different antipsychotic medications
Relevant history or current presence of any significant and/or unstable cardiovascular, respiratory, neurological (including seizures or significant cerebrovascular), renal, hepatic, hematological, endocrine, immunological, or other systemic disease
Biochemistry, hematology, or urinalysis test results outside the normal reference range and considered by the investigator to be clinically significant
History or evidence of clinically significant hepatic disease (including aspartate aminotransferase or alanine aminotransferase values >2 times the upper limit of normal) at screening
Neuroleptic malignant syndrome
Significant risk of suicidal, homicidal, or violent ideation or behavior, according to the investigator's clinical assessment
Known or suspected hypersensitivity or intolerance to risperidone, paliperidone, Intralipid, or any of their excipients
Previously received an injection of paliperidone palmitate, treatment with a long-acting injectable antipsychotic or electroconvulsive therapy within 60 days of screening, nonselective, or irreversible monoamine oxidase inhibitor antidepressants within 4 weeks of screening
Receipt of other antidepressant agents, unless the patient had been receiving a stable dose for 30 days before screening
Receipt of oral antipsychotic agents within 2 days before baseline, mood stabilizers (including lithium, valproic acid, carbamazepine, lamotrigine, and topiramate) within 2 days before baseline, β-blockers, except when used to control hypertension and if the patient's blood pressure was stabilized before screening, or other prescription, over-the-counter, or herbal agents with psychoactive properties within 2 days of baseline
Exposure to any experimental drug, experimental biologic agent, or experimental medical device within 30 days before screening, or previous participation in the current study

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; PANSS, Positive and Negative Syndrome Scale.

All efficacy analyses used the ITT analysis set. For the change in PANSS total score at end point, least-squares adjusted means were calculated for each active treatment group *vs* placebo, using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline score as a continuous covariate. The closed testing procedure using Dunnett's test was applied to adjust for multiple testing of paliperidone palmitate doses *vs* placebo. Exploration of the treatment-by-country interaction was prespecified at a 0.10 significance level. A mixed model repeated measures (MMRM) analysis was performed as a sensitivity analysis, using observed case data for the change from baseline in PANSS total score. A similar ANCOVA model as described above was used for the change at end point in CGI-S (on ranked changes), PSP, PANSS negative, positive, and general psychopathology subscales, and PANSS Marder factor scores. The Bonferroni–Holm step-down testing procedure was applied to the analysis of the change in CGI-S (ranked changes) and PSP scales to adjust for multiple comparisons. No adjustment was made for multiple comparisons for other efficacy variables. Differences between treatment groups in the percentages of responders were evaluated using the Cochran–Mantel–Haenszel test, controlling for country. A Kaplan–Meier plot of the estimated time to discontinuation due to lack of efficacy was presented by the treatment group to assess the consistency with other efficacy findings.

Safety analyses were based on the safety analysis set and summarized using descriptive statistics. Treatment-emergent adverse events were summarized according to the Medical Dictionary for Regulatory Activities system organ class and preferred term.

Adjusting for multiple comparisons of the three paliperidone palmitate dose groups with placebo (two-sided α-level 0.05), 110 patients in each group were required to detect a treatment difference of 10 points with a power of 90%. Adjusted for a rate of 8% of patients without either baseline or postbaseline efficacy assessments, 120 patients were required per treatment group.

RESULTS

Patients

Demographics and patient characteristics were well balanced across treatment groups, with 514 patients (99% of those randomized) included in the ITT analysis set (Table 2).

Of the 518 randomized patients, 263 (51%) patients completed the 13-week double-blind period. The safety analysis set included $>99\%$ of all randomized patients ($n=517$). Reasons for and rates of early withdrawal showed no apparent differences across groups, with the exception of withdrawals due to lack of efficacy. More patients in the placebo group (35%) discontinued because of lack of efficacy than in the paliperidone palmitate treatment groups, with the paliperidone 100 mg equiv. group having the lowest rate of discontinuation because of lack of efficacy (16 *vs* 24% for both the 25- and 50-mg groups) (Figure 1). Kaplan–Meier estimates of time to discontinuation because of lack of efficacy are shown (Figure 2).

Efficacy

Primary outcome: PANSS total score. On the basis of the LOCF ANCOVA analysis at end point, PANSS total scores for all paliperidone palmitate groups improved significantly *vs* placebo (multiplicity adjusted, 25 mg equiv., $p=0.015$;

Table 2 Demographic and Baseline Characteristics (Intent-To-Treat Analysis Set)

Variable	Placebo ($n=125$)	Paliperidone palmitate			
		25 mg equiv. (39 mg) ($n=130$)	50 mg equiv. (78 mg) ($n=128$)	100 mg equiv. (156 mg) ($n=131$)	Total ($n=514$)
Age, years (mean ± SD)	41.1 ± 11.8	40.8 ± 10.6	39.0 ± 11.9	42.3 ± 10.7	40.8 ± 11.3
Sex, %					
Men	62	65	73	65	67
Women	38	35	27	35	33
Race, %					
White	67	67	69	65	67
Black	28	29	26	31	29
Asian	1	2	2	1	1
Other	4	2	3	3	3
Weight, kg (mean ± SD)	81.7 ± 22.7	81.7 ± 23.5	80.8 ± 21.2	81.2 ± 20.8	81.4 ± 22.0
BMI, kg/m^2 (mean ± SD)	27.5 ± 6.6	27.6 ± 7.6	27.3 ± 7.2	27.7 ± 6.4	27.5 ± 7.0
Schizophrenia type, %					
Paranoid	92	92	89	89	90
Disorganized	1	1	2	2	2
Catatonic	1	0	1	0	<1
Undifferentiated	6	7	8	9	8
Age at diagnosis, years (mean ± SD)	26.9 ± 9.6	26.5 ± 9.1	24.5 ± 8.5	27.4 ± 9.6	26.3 ± 9.2
Baseline PANSS total score (mean ± SD)	90.7 ± 12.2	90.6 ± 12.2	91.2 ± 12.0	90.8 ± 11.7	90.8 ± 12.0
Baseline CGI-S, %					
Very mild	1	0	0	0	<1
Mild	1	2	2	3	2
Moderate	54	45	45	51	49
Marked	39	47	44	37	42
Severe	6	6	9	9	7
Previous hospitalizations, %					
0	6	2	5	6	5
1	22	17	26	21	21
2	12	15	19	11	14
3	11	15	10	22	15
⩾4	49	50	40	40	45

Abbreviations: BMI, body mass index; CGI-S, Clinical Global Impression-Severity Scale; PANSS, Positive and Negative Syndrome Scale.

50 mg equiv., $p=0.017$; and 100 mg equiv., $p<0.001$) (Figure 3). The MMRM analysis corroborated these findings as all three doses of paliperidone palmitate resulted in significant improvement *vs* placebo overall ($p\leqslant0.019$), as well as on day 92 ($p\leqslant0.021$). None of the pairwise comparisons between active treatment groups were significant. The primary efficacy LOCF analysis showed a statistically significant treatment-by-country interaction ($p=0.02$). Patients enrolled at sites outside the United States had greater improvements in PANSS total scores than did those from US sites. US sites contributed the largest percentage of patients (55%) to the ITT analysis set, followed by Russia (31%), Bulgaria (7%), Romania (4%), and South Africa (3%). Demographic and baseline characteristics were examined to determine whether any imbalance across treatment groups and countries occurred. Subsequently, a notable disparity was detected in the distribution of baseline BMI across countries, but not across treatment groups: 74% of US patients were obese (BMI $\geqslant30$ kg/m^2) or overweight (BMI $\geqslant25$ and <30 kg/m^2), whereas 42% of Romanian, 41% of Russian, 35% of Bulgarian, and 23% of South African patients were either

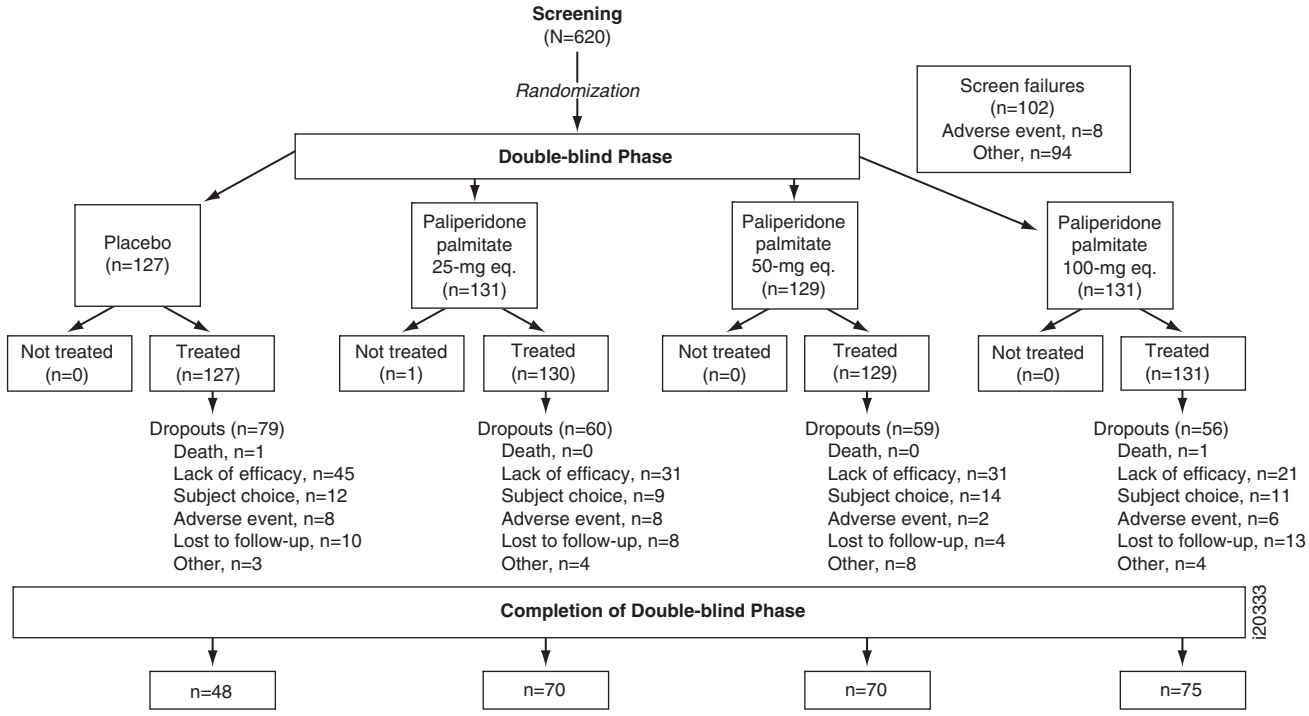

Figure 1 Study design. The doses expressed as paliperidone palmitate 25, 50, and 100 mg equiv. equate to 39, 78, and 156 mg, respectively, of paliperidone palmitate. One patient assigned to the paliperidone palmitate 25 mg equiv. group was excluded by the medical monitor on the day of randomization, due to hypotension, and hence did not receive any double-blind medication.

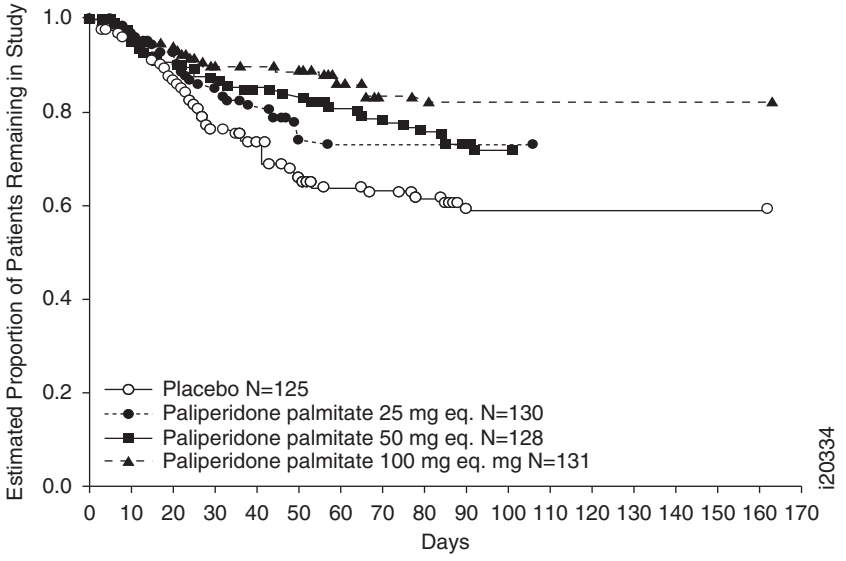

Figure 2 Kaplan–Meier estimates of time to withdrawal due to lack of efficacy (intent-to-treat analysis set). The doses expressed as paliperidone palmitate 25, 50, and 100 mg equiv. equate to 39, 78, and 156 mg, respectively, of paliperidone palmitate.

obese or overweight. The mean BMI at baseline in the US was 30.2 kg/m^2 (range: 17–60 kg/m^2) compared with 24.2 kg/m^2 (range: 16–38 kg/m^2) in the non-US regions. An exploratory ANCOVA, on the change in PANSS total score, with treatment, country, BMI, and treatment-by-BMI interaction as factors, and baseline PANSS total score as a covariate was performed. The interaction of BMI on the treatment effect was suggestive of a differential treatment effect by BMI category, as it approached the statistical significance level of 0.10 ($p = 0.14$). Hence, the heterogeneous treatment effect across BMI categories was considered a key contributor to the treatment-by-country interaction, given the disparity in BMI distribution across countries.

Secondary and other efficacy outcomes. CGI-S scores, and PANSS positive, negative, and general psychopathology subscale scores, and PANSS positive symptoms and

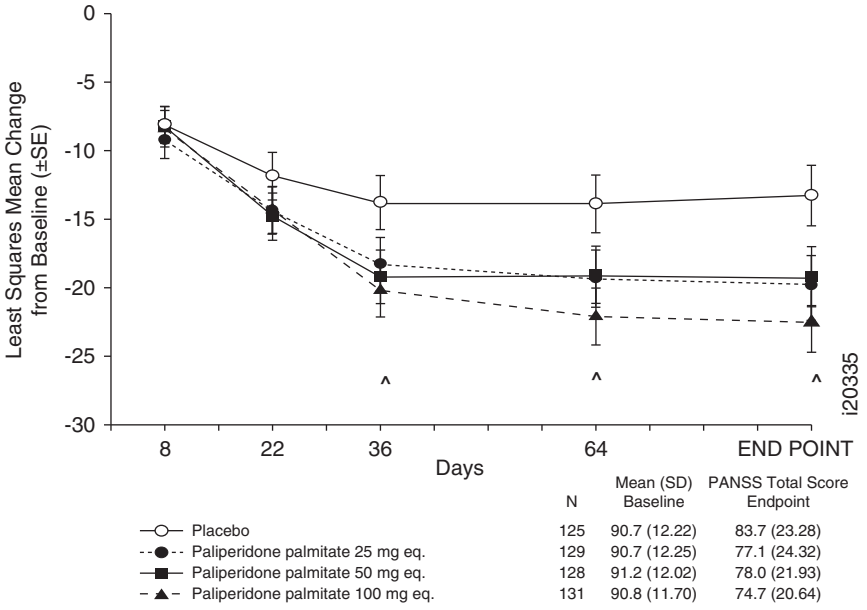

Figure 3 Onset of effect: least-squares mean change in PANSS total score over time (intent-to-treat analysis set). Mean (SD) changes in PANSS total scores from baseline to end point were −13.6 (21.45) for the 25-mg group, −13.2 (20.14) for the 50-mg group, and −16.1 (20.36) for the 100-mg equiv. group, *vs* −7.0 (20.07) for placebo. The mean (SD) values reported below the graph are absolute means and not adjusted for the covariates. The doses expressed as paliperidone palmitate 25, 50, and 100 mg equiv. equate to 39, 78, and 156 mg, respectively, of paliperidone palmitate. ^All unadjusted *p*-values <0.05 as early as day 36, for all three doses of paliperidone palmitate.

negative symptoms Marder factor scores significantly improved *vs* placebo for all paliperidone groups, whereas PSP scores did not (Table 3).

On the basis of the 30% response criterion, significantly more patients in the paliperidone palmitate 25 mg equiv. (45.7%; $p=0.015$) and 100 mg equiv. (51.9%; $p<0.001$) groups were treatment responders than those in the placebo group (31.2%). The paliperidone palmitate 50 mg equiv. group (37.5%) did not differ statistically ($p=0.27$ *vs* placebo).

Safety

Adverse events. Overall, treatment-emergent adverse events occurred at similar rates among the paliperidone palmitate (66–75%) and placebo (72%) groups. The incidences of adverse events occurring in $\geqslant 5\%$ of patients in any group were generally similar for paliperidone palmitate and placebo, except that weight increase (4% paliperidone palmitate overall *vs* 0% placebo) and somnolence (4% paliperidone palmitate overall *vs* 1% placebo) occurred more frequently (with $\geqslant 3\%$ difference) with paliperidone palmitate treatment (Figure 4).

The incidence of serious treatment-emergent adverse events was higher in the placebo group (18%) than in any of the paliperidone palmitate groups (8–14%). Two patients died during the study. One patient in the paliperidone palmitate 100 mg equiv. group committed suicide on day 58, 22 days after the third injection of study medication and 1 patient in the placebo group died as a result of pancreatic carcinoma on day 66, after receiving all 4 doses of study medication. The incidence of treatment-emergent adverse events leading to discontinuation was lower in the paliperidone palmitate 50 mg equiv. group (2%) than in any of the other treatment groups (5–6%). The adverse events that most often led to discontinuation were schizophrenia worsening and agitation.

Extrapyramidal symptoms. The incidence of treatment-emergent EPS events was low. Parkinsonism was the most frequent category and was reported at a similar rate in the placebo (5%) and overall paliperidone palmitate groups (6%). None of the events in paliperidone palmitate-treated patients were severe or serious, and no patient discontinued treatment as a result. The percentage of patients receiving anti-EPS medications decreased from before the double-blind period to the end of the study in all treatment groups: from 31 to 6% for placebo, from 31 to 7% for paliperidone palmitate 25 mg equiv., from 38 to 4% for paliperidone palmitate 50 mg equiv., and from 27 to 6% for paliperidone palmitate 100 mg equiv. There were no clinically relevant differences between the paliperidone palmitate groups and placebo in changes in BARS, SAS, or AIMS scores and generally no statistically significant differences (Table 4).

Laboratory values and vital signs. Increases in prolactin levels occurred with greater frequency in paliperidone palmitate-treated patients and were dose related. The mean change (SD) from baseline to end point in men *vs* women was: placebo, −2.1 (1.7) *vs* −8.8 (7.4); 25 mg equiv., 4.0 (2.4) *vs* 9.3 (5.5), 50 mg equiv., 6.8 (2.2) *vs* 35.1 (6.7); and 100 mg equiv., 10.4 (2.2) *vs* 43.6 (7.7) ng/ml. The incidence of spontaneously reported potentially prolactin-related treatment-emergent adverse events was low: 1–2% of paliperidone palmitate-treated patients and 1% of placebo patients. These events included erectile dysfunction (1% for placebo and 1% for paliperidone palmitate 100 mg equiv.), galactorrhea (1% for paliperidone palmitate 100 mg equiv.),

Table 3 Secondary Efficacy Variables (Intent-To-Treat Analysis Set)

Efficacy measure	Placebo	Paliperidone palmitate		
		25 mg equiv. (39 mg)	50 mg equiv. (78 mg)	100 mg equiv. (156 mg)
PANSS positive subscale, mean ± SD[a]				
N	125	129	128	131
Baseline	22.4 ± 4.8	23.2 ± 4.7	23.0 ± 4.4	22.7 ± 4.4
Change from baseline	−1.6 ± 7.0	−4.0 ± 7.5	−3.8 ± 6.9	−4.8 ± 6.2
p-value	—	0.010	0.017	<0.001
PANSS negative subscale, mean ± SD[a]				
N	125	129	128	131
Baseline	24.4 ± 4.5	23.6 ± 4.9	24.0 ± 5.0	23.9 ± 4.5
Change from baseline	−2.3 ± 5.1	−3.5 ± 5.1	−3.5 ± 5.9	−3.9 ± 5.6
p-value	—	0.019	0.053	0.005
General psychopathology, mean ± SD[a]				
N	125	129	128	131
Baseline	43.9 ± 6.5	43.9 ± 6.8	44.2 ± 7.0	44.1 ± 6.7
Change from baseline	−3.1 ± 10.2	−6.1 ± 10.9	−6.0 ± 10.2	−7.4 ± 10.4
p-value	—	0.019	0.034	<0.001
CGI-S, median (range)[b]				
N	125	129	128	131
Baseline	4.0 (2, 6)	5.0 (3, 6)	5.0 (3, 6)	4.0 (3, 6)
Change from baseline	0 (−3, 2)	−1.0 (−5, 2)	−1.0 (−3, 2)	−1.0 (−4, 2)
p-value	—	0.003	0.006	0.002
PSP score, mean ± SD[b]				
N	118	119	121	119
Baseline	48.0 ± 12.6	47.7 ± 12.2	46.3 ± 12.6	45.9 ± 12.0
Change from baseline	3.6 ± 17.1	6.5 ± 15.6	6.8 ± 15.4	7.4 ± 14.6
p-value	—	0.154	0.189	0.110
PANSS Marder factor scores, mean ± SD[a]				
N	125	129	128	131
Positive symptoms				
Baseline	26.1 ± 4.9	27.2 ± 5.0	27.0 ± 4.8	27.0 ± 4.8
Change from baseline	−2.0 ± 6.7	−5.0 ± 7.6	−4.4 ± 6.4	−5.5 ± 6.5
p-value	—	<0.001	0.010	<0.001
Negative symptoms				
Baseline	23.2 ± 4.7	22.2 ± 5.3	22.7 ± 5.8	22.9 ± 5.1
Change from baseline	−2.4 ± 5.2	−3.8 ± 5.2	−3.5 ± 6.4	−3.9 ± 5.8
p-value	—	0.003	0.041	0.007
Disorganized thoughts				
Baseline	21.2 ± 4.5	21.3 ± 4.5	21.4 ± 4.9	20.9 ± 4.3
Change from baseline	−2.1 ± 5.0	−2.7 ± 5.3	−3.0 ± 5.1	−3.1 ± 5.3
p-value	—	0.343	0.198	0.067
Uncontrolled hostility/excitement				
Baseline	9.0 ± 3.0	9.4 ± 3.2	9.6 ± 3.4	9.1 ± 3.3
Change from baseline	0.7 ± 4.3	−0.3 ± 4.2	−0.8 ± 4.5	−1.1 ± 4.0
p-value	—	0.096	0.013	<0.001
Anxiety/depression				
Baseline	11.2 ± 3.3	10.6 ± 3.3	10.5 ± 2.8	11.0 ± 3.3
Change from baseline	−1.2 ± 3.2	−1.7 ± 3.5	−1.5 ± 3.4	−2.3 ± 3.1
p-value	—	0.041	0.127	<0.001

Abbreviations: CGI-S, Clinical Global Impression-Severity Scale; PSP, Personal and Social Performance Scale; PANSS, Positive and Negative Syndrome Scale.
[a]*p*-values unadjusted for multiple comparisons.
[b]*p*-values adjusted for multiplicity using the Bonferroni–Holm step-down procedure.

decreased libido (1% for placebo), and sexual dysfunction (1% for paliperidone palmitate 50 mg equiv. and 2% for paliperidone palmitate 100 mg equiv.).

Mean body weight and mean BMI increased in a dose-related manner in the paliperidone palmitate groups, compared with mean decreases for placebo (Table 5). Except for prolactin, there were no clinically relevant mean changes from baseline to any time point for laboratory analytes, including renal function, liver function, serum lipids, or glucose, and none from baseline to end point in vital signs. No patient had a maximum linear-derived corrected QT interval (QTcLD) value >480 ms or a maximal change in QTcLD >60 ms at any time point during the study. The mean (SD) changes from baseline to end point in QTcLD were 0.7 (13.3) ms for placebo, 0.2 (12.1) ms for paliperidone palmitate 25 mg equiv., 1.7 (14.0) ms for paliperidone palmitate 50 mg equiv., and 0.2 (13.3) m for paliperidone palmitate 100 mg equiv.

Injection-site tolerability. Patient evaluations of injection-site pain, as measured by a visual analog scale (0 mm (no pain) to 100 mm (maximum pain)), were similar across treatment groups, and pain scores decreased with time. The day 1 and day 92 injection-site mean pain scores for placebo-treated patients were 8.3 and 1.2 mm, respectively. For patients treated with paliperidone palmitate, the day 1 and day 92 injection-site mean pain scores were 6.9 and 0.7 mm (25 mg equiv. dose group); 6.6 and 3.5 mm (50 mg equiv. dose group); and 5.8 and 1.4 mm (100 mg equiv. dose group), respectively.

Investigators reported injection-site pain during the study as absent (86–100%), mild (0–12%), or moderate to severe (0–2%) for paliperidone palmitate-treated patients. They reported similar scores for placebo-treated patients: absent (87–100%), mild (0–13%), or moderate to severe (0–2%). Investigator evaluations also showed that occurrences of

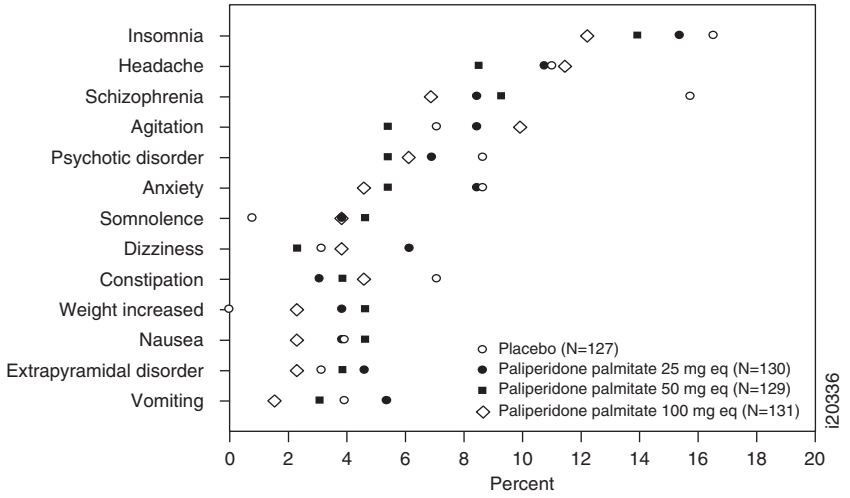

Figure 4 Treatment-emergent adverse events experienced by ⩾5% of patients in any treatment group. The doses expressed as paliperidone palmitate 25, 50, and 100 mg equiv. equate to 39, 78, and 156 mg, respectively, of paliperidone palmitate.

Table 4 Change from Baseline in Extrapyramidal Symptom Rating Scale Scores (Safety Analysis Set)

Scale	Placebo ($n=127$)[a]	Paliperidone palmitate		
		25 mg equiv. (39 mg) ($n=130$)[a]	50 mg equiv. (78 mg) ($n=129$)[a]	100 mg equiv. (156 mg) ($n=131$)
SAS				
Change from baseline, median (range)	0.0 (−1, 1)	0.0 (−1, 1)	0.0 (−2, 2)	0.0 (−1, 0)
SAS *p*-value (minus placebo)[a]		0.418	0.045	0.119
BARS				
Global clinical rating of akathisia at end point, %				
Absent	88.0	91.5	88.3	84.7
Questionable	7.2	3.9	5.5	9.2
Mild	3.2	3.1	6.3	3.8
Moderate	1.6	1.6	0	2.3
BARS *p*-value (*vs* placebo)[b]		0.301	0.943	0.400
AIMS				
Change from baseline, median (range)	0.0 (−4, 5)	0.0 (−8, 9)	0.0 (−7, 6)	0.0 (−5, 4)
AIMS *p*-value (minus placebo)[c]		0.413	0.581	0.583

Abbreviations: SAS, Simpson Angus Scale; BARS, Barnes Akathisia Rating Scale; AIMS, Abnormal Involuntary Movement Scale.
All comparisons with placebo without multiplicity adjustment.
[a]For SAS and AIMS scores: actual patients analyzed were $n=125$ for placebo; 129 for 25 mg equiv.; and 128 for 50 mg equiv. dose groups.
[b]Comparison with placebo based on Cochran–Mantel–Haenszel test with rank scores controlling for country.
[c]Comparisons with placebo based on ANOVA model on the ranks for the change at end point with treatment and country as factors.

Table 5 Change from Baseline to End Point for Body Weight and Body Mass Index (Safety Analysis Set)

	Placebo	Paliperidone palmitate		
		25 mg equiv. (39 mg)	50 mg equiv. (78 mg)	100 mg equiv. (156 mg)
Body weight	$n=111$	$n=116$	$n=122$	$n=112$
Mean ± SD, kg	−0.5 ± 4.83	0.4 ± 4.01	0.8 ± 3.29	1.3 ± 3.35
Body mass index	$n=111$	$n=116$	$n=122$	$n=112$
Mean ± SD, kg/m^2	−0.1 ± 1.98	0.2 ± 1.37	0.3 ± 1.13	0.5 ± 1.15

redness, induration, or swelling were infrequent, generally mild, decreased over time, and similar in incidence for the paliperidone palmitate and placebo groups.

DISCUSSION

LAI preparations offer important options for treatment of chronic diseases and are particularly important for enhancing adherence, which may in turn benefit treatment outcomes and quality of life (Bhanji *et al*, 2004; Love, 2002; Marinis *et al*, 2007; Nasrallah *et al*, 2004). Adherence to treatment is probably a major reason for the lower risk for relapse with LAI formulations *vs* oral antipsychotic therapy. With LAI formulations, there is greater interaction between the patient and the health-care provider. The provider knows when a patient misses an injection and has the opportunity to intervene because the sustained medication delivery provides a time window to follow-up with the patient. There are several other advantages of LAI formulations. If a relapse does occur, the health-care practitioner can determine whether it is the result of poor patient adherence or due to the disease process (Kane *et al*, 2003). LAIs also provide relatively stable plasma levels of drug once steady state is achieved and generally offer improved tolerability over oral formulations. Despite these advantages, LAIs remain underused (Nasrallah, 2007).

This randomized, placebo-controlled, 13-week double-blind study showed that paliperidone palmitate (25, 50, and 100 mg equiv.), a long-acting atypical injectable antipsychotic, significantly improved the PANSS total score compared with placebo, as well as CGI-S, PANSS Marder factor scores, and responder rates when administered once monthly, without oral supplementation, into the gluteal muscle in patients with symptomatic schizophrenia. The PSP scale, a validated scale that assesses personal and social functioning (Nasrallah *et al*, 2008; Morosini *et al*, 2000; Patrick *et al*, 2009) did not show a significant treatment difference, perhaps due to the high placebo response observed in this study.

The incidence of treatment-emergent EPS-related adverse events was low in paliperidone palmitate-treated patients. There were no clinically important increases in lipids or glucose levels seen in this 13-week study. However, mean body weight and mean BMI increased in a dose-related manner in paliperidone palmitate-treated patients. Dose-related increases in prolactin levels also occurred in paliperidone palmitate-treated patients. The incidence of spontaneously reported potentially prolactin-related adverse events was low ($\leqslant$2%), although relying on spontaneous reports may result in underreporting of actual cases of sexual dysfunction.

Prolongation of the QT intervals remains a concern with the use of antipsychotics (Taylor, 2003). In this study, there was no evidence of clinically significant QTc prolongation with paliperidone palmitate at doses up to 100 mg equiv. Change from baseline in QTcLD values was similar across all treatment groups.

Investigator evaluations of injection-site pain, swelling, redness, and induration, as well as patient evaluations of injection-site pain during this study, suggest that paliperidone palmitate is well tolerated locally, with minimal pain or injection-site reactions.

These results are generally consistent with those from other recent studies of paliperidone palmitate for both the acute and maintenance treatment of patients with schizophrenia (Gopal *et al*, 2010; Hough *et al*, 2008, 2009; Kramer *et al*, 2010), as well as for the oral formulation, paliperidone (Davidson *et al*, 2007; Kane *et al*, 2007; Kramer *et al*, 2007; Luthringer *et al*, 2007; Marder *et al*, 2007). Although in this study, paliperidone palmitate was administered gluteally, it may be administered in the deltoid muscle as well (Hough *et al*, 2009). This offers an additional advantage in supporting patient preference for injection site.

In this study, a once-monthly dosing regimen with paliperidone palmitate doses of 25, 50, and 100 mg equiv. produced clinically meaningful and statistically significant improvement in efficacy measures in patients with symptomatic schizophrenia. The tolerability profile of paliperidone palmitate may offer additional advantages in helping to ensure treatment adherence.

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DISCLOSURE

This study was funded by Johnson & Johnson Research & Development, LLC, Raritan, NJ, who was responsible for study design; in the collection, analysis, and interpretation of the data; in the writing of the report; and in the decision to submit the paper for publication. Dr Nasrallah was an investigator in this study and over the past 3 years has received research grant support from Johnson & Johnson Pharmaceutical Research & Development to conduct FDA studies and investigator-initiated studies, and has received consultation fees and speaker honoraria as well. He has also received grants, or participated in speakers bureaus or advisory boards for the following pharmaceutical

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Author Contributions: HAN was a principal investigator and the coordinating investigator for this study and contributed to data collection and interpretation and literature analysis. SG, JAQ, ME, EY, and DH contributed to study design and data interpretation. DH and SG wrote the protocol. CG-M and PL contributed to study design, and data analysis and interpretation. All authors contributed to writing and reviewing this report and approved the final paper.

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