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Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled study ☆

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ABSTRACT

Objective: We assessed efficacy and tolerability of the injectable atypical antipsychotic paliperidone palmitate in delaying time-to-relapse in adults with schizophrenia.
Methods: Eligible patients (Positive and Negative Syndrome Scale [PANSS] total score<120) were transitioned from previous antipsychotics to paliperidone palmitate during a 9-week, open-label phase. Patients received the first 2 intramuscular injections of paliperidone palmitate (50 mg eq) one-week apart, then subsequent injections (25, 50, or 100 mg eq, flexibly-dosed), once-monthly. Stable patients (PANSS total score ≤75) continued into the 24-week maintenance phase. At maintenance phase endpoint, stabilized patients were randomized (1:1 ratio) to either continue paliperidone palmitate (at stabilized dose) or begin placebo in the variable-duration, double-blind phase.
Results: The preplanned interim analysis (conducted after 68 relapse events) included 312 patients: mean age = 40 years, 55% men, 66% white, and mean transition baseline PANSS total score (SD): placebo, 69.5 (16.89); paliperidone palmitate, 69.3 (17.39). Time-to-relapse (primary endpoint) favored paliperidone palmitate ($p<0.0001$, log-rank test) at interim and final analysis ($n=408$). The hazard ratio (placebo/paliperidone palmitate) at the final analysis was 3.60 (95% CI: 2.45, 5.28). Treatment-emergent adverse event rates (final analysis set) were: 67% for transition and maintenance phases, and 45% (placebo) and 44% (paliperidone palmitate) for the double-blind phase. Across phases, the incidence of glucose-related adverse events was low (≤4%), while mean weight increased by 1.9 kg for paliperidone palmitate and remained unchanged for placebo patients. Injection site tolerability was comparable between groups.
Conclusion: Paliperidone palmitate significantly delayed time-to-relapse compared with placebo and presented no new safety signals.

1. Introduction

The chronic nature of schizophrenia, coupled with cognitive impairment, lack of insight, and frequent relapse of acute psychotic symptoms results in an illness that offers significant treatment challenges. Poor adherence to, or discontinuation of, potentially effective antipsychotic therapy substantially increases the risk for relapse in patients with schizophrenia (Keith et al., 2004). Long-acting injectable (LAI) antipsychotics offer the opportunity to establish long-

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term control in patients (Kucukalic et al., 2007; Nasrallah and Lasser, 2006). They provide consistent drug levels that are sustained over weeks and missed injections are immediately known, permitting the medical team the opportunity for intervention (Kane, 2007; Nasrallah and Lasser, 2006).

Paliperidone palmitate, an atypical antipsychotic agent, is the palmitate ester of paliperidone and is designed to be administered as a once-monthly intramuscular injection. The efficacy and safety of the oral extended-release formulation in the acute and maintenance treatment of schizophrenia have been demonstrated (Marder et al., 2007; Kane, 2007; Kramer et al., 2007). Several studies have also demonstrated efficacy and safety of paliperidone palmitate in patients with acute schizophrenia (Nasrallah et al., 2008a; Pandina et al., submitted for publication). Following an initial dosing regimen administered in the deltoid, patients rapidly and consistently obtain therapeutic plasma levels (Samtani et al., 2009a,b) and plasma concentrations can be subsequently maintained using either deltoid or gluteal injections (Hough et al., 2009; Samtani et al., 2009c). Oral supplementation is not required during dosing (Samtani et al., 2009a,b). Paliperidone palmitate was recently approved in the United States for the acute and maintenance treatment of schizophrenia. The current double-blind randomized study evaluated its efficacy and safety in delaying time-to-relapse in patients with schizophrenia and supports the maintenance indication.

2. Materials and methods

2.1. Patients

Men and women, aged 18–65 years (inclusive), with a diagnosis of schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [DSM-IV], criteria) for at least 1 year before screening, and a Positive and Negative Syndrome Scale (PANSS) total score below 120, at screening and baseline were enrolled. Both symptomatic and stable patients were eligible.

Major exclusion criteria were: primary, active DSM-IV (American Psychiatric Association, 1994) diagnosis other than schizophrenia; significant risk of suicidal or aggressive behavior; history of substance dependence within 3 months before screening; significant medical conditions, or treatment resistance (failure to respond to 2 adequate trials, minimum 4 weeks of antipsychotic medications); use of any 4-week depot antipsychotic within 28 days or risperidone LAI within 5 weeks before screening; use of oral antipsychotics, mood stabilizers, or other prescription or over-the-counter drugs within 2 days before baseline; or involuntary admission to a psychiatric hospital. Women were excluded if pregnant, nursing, or planning to become pregnant.

The independent ethics committee or institutional review board at each study site approved the protocol and the study was conducted in accordance with the ethical principles in the Declaration of Helsinki, consistent Good Clinical Practices and applicable regulatory requirements. All participants provided written informed consent.

2.2. Study medication

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

Paliperidone palmitate was provided as prefilled syringes containing 25, 50, or 100 mg eq paliperidone palmitate (or matching placebo [Intralipid® 20% injectable emulsion]). Injections were administered in the gluteal muscle, alternating the location side (left or right) at each injection.

Oral tolerability medication (paliperidone extended release [ER], 3 mg) was administered for 4 days during the screening period to patients without previous documented exposure to risperidone or paliperidone.

2.3. Study design, randomization, and blinding

This study, conducted from March 4, 2005 to February 16, 2007 (up through the double-blind phase), included patients from 56 centers in 9 countries. There were 5 phases (Fig. 1): screening and oral tolerability testing phase (up to 7 days), a 9-week open-label transition phase during which eligible patients (PANSS total score <120) were switched from their previous antipsychotic and received once-monthly injections of flexibly-dosed paliperidone palmitate (25, 50, or 100 mg eq) after an initial regimen of paliperidone palmitate 50 mg eq on days 1 and 8; a 24-week open-label maintenance phase during which stable patients (PANSS score ≤ 75 at week 9) received flexibly-dosed paliperidone palmitate (25, 50, or 100 mg eq) for the first 12 weeks, with dose adjustments based on patient's clinical need, followed by 12-weeks of treatment at the established maintenance dose; a variable-duration, event-driven double-blind phase, when stabilized patients with PANSS total score ≤ 75 and selected PANSS item scores ≤ 4 (P1 [delusions], P2 [conceptual disorganization], P3 [(hallucinatory behavior)], P6 [suspiciousness/persecution], P7 [hostility], G8 [uncooperativeness] and G14 [poor impulse control]) were randomized in a 1:1 ratio (via a sponsor-prepared computer-generated randomization scheme; assigned by an interactive voice-response system) to receive either paliperidone palmitate (at the previously stabilized dose), or placebo; and an optional 52-week open-label extension phase.

Patients remained in the double-blind phase until they experienced a relapse, withdrew from the study, or until the study was completed. An interim analysis for efficacy was preplanned to occur after 68 relapse events (as defined in Section 2.5). We report here the results through the end of the double-blind phase.

An Independent Data Monitoring Committee (IDMC) performed ongoing safety monitoring, evaluated efficacy at the interim analysis, and provided recommendations about modifying, stopping, or continuing the study.

2.4. Assessments

The primary efficacy variable was the time-to-first relapse during the double-blind phase. Relapse was defined as one or more of the following: (1) hospitalization for symptoms of schizophrenia (involuntary or voluntary admission), (2) 25% increase in PANSS total score for two consecutive assessments for patients who scored >40 at randomization, or a 10-point increase for patients who scored ≤ 40 at randomization,

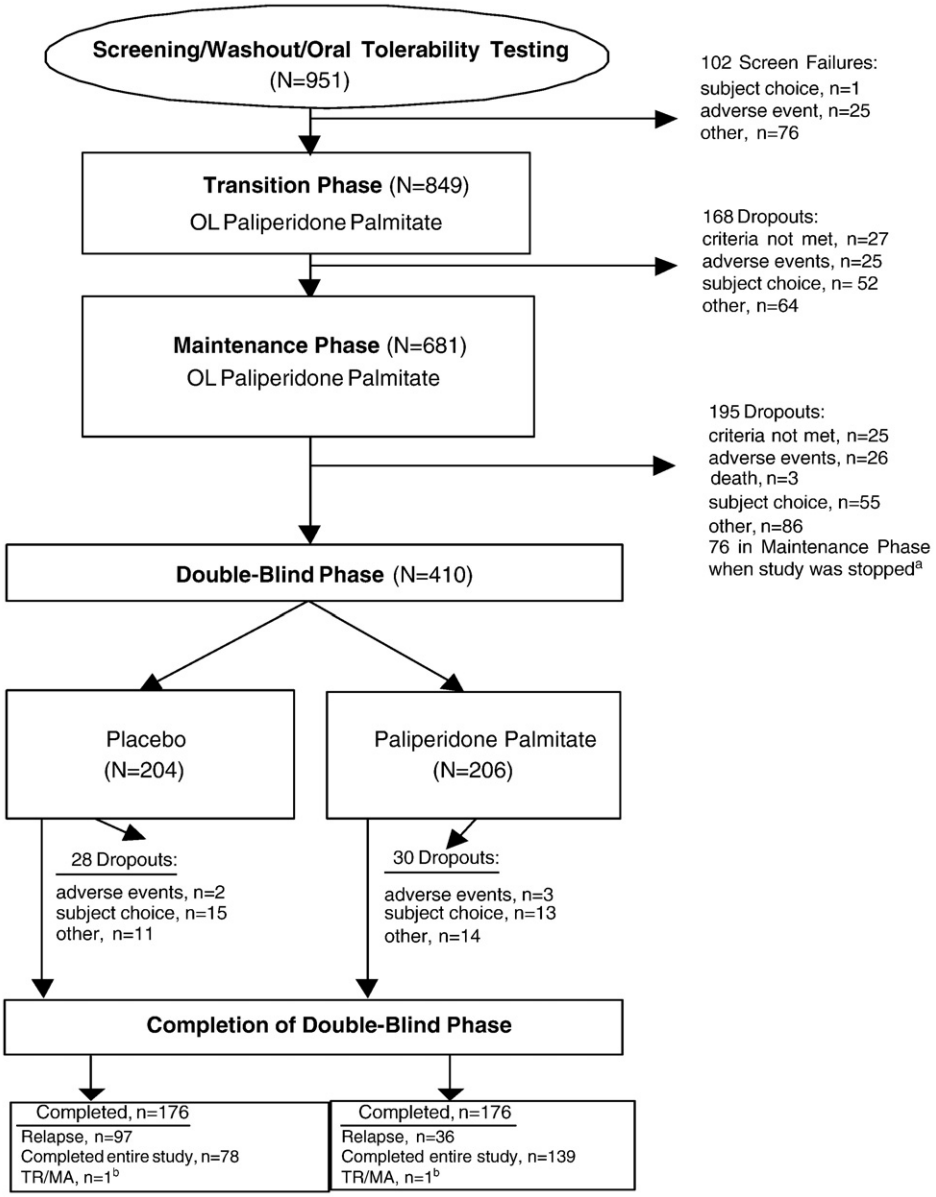


Fig. 1. Study flow and patient disposition. [a]At the time the study was stopped 76 patients (9% of the 849 enrolled patients) were in the maintenance phase and considered as completing the entire study, per protocol. [b]One patient in each treatment group was randomized, but was in the transition/maintenance phase when the study was stopped and did not receive any double-blind injections. Note: screening phase included a 4-day oral tolerability test for patients who had not previously received at least 4 doses of either oral risperidone or paliperidone, or 1 dose of risperidone long-acting injectable. Date of planned interim analysis: January 23, 2007 (data cut-off; September 25, 2006).OL = open-label; TR = transition; MA = maintenance.

(3) deliberate self-injury or aggressive behavior, or suicidal or homicidal ideation and aggressive behavior that was clinically significant, and (4) increase for two consecutive assessments in prespecified individual PANSS items scores (P1, P2, P3, P6, P7 and G8) to ≥ 5 for patients whose score was ≤ 3 at randomization, or to ≥ 6 for patients whose score was 4 at randomization. Secondary efficacy measures included changes from double-blind baseline to endpoint in: PANSS total score and factor scores, Clinical Global Impression-Severity (CGI-S) score, and Personal and Social Performance (PSP) Scale scores.

Safety assessments included treatment-emergent adverse events (TEAEs), extrapyramidal symptom (EPS) rating scales (Barnes, 1989; Guy, 1976; Simpson and Angus, 1970) clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms, physical examination findings, and investigators' and patients' evaluation of the injection site.

2.5. Statistical analyses

The study was to be stopped if efficacy was established (at a significance level of 0.0106) at the preplanned interim analysis

after 68 relapse events. Otherwise, the study was to continue until 136 events had occurred, with the final analysis performed at a significance level of 0.0448. This study had 90% power to detect a 15% difference between 10-month relapse rates for placebo (40%) and paliperidone palmitate (25%) with a significance level of 0.05 (two-sided). Kaplan–Meier methodology was used to assess the primary efficacy variable (time-to-relapse), and the log-rank test (two-sided) was used to compare treatment differences. Cox proportional hazard models were constructed to individually examine the impact of various factors (age, sex, body mass index (BMI), and geographic region) upon the primary efficacy results. All secondary efficacy analyses were performed at the 0.05 level (two-sided) across treatment groups with no adjustments for multiplicity, using the last observation carried forward approach.

2.6. Populations assessed

Efficacy and safety analyses for the transition and maintenance phases used the all treated analysis set, which included all patients who received at least one dose of paliperidone palmitate in the transition phase. All efficacy analyses (interim and final) from the double-blind phase used the intent-to-treat (ITT) analysis set, which included all randomized patients who received at least one injection in the double-blind phase and had data available at the time of interim analysis cut-off date or through study completion date. Safety analysis set for the double-blind phase was the same as the ITT analysis set.

3. Results

Following the preplanned interim analysis, the IDMC recommended early study termination based on significant ($p<0.0001$) interim efficacy results in favor of paliperidone palmitate for time-to-relapse. Consequently, the interim analysis became the primary analysis, per protocol. The final analysis, based on all the data from start of the study through completion of the double-blind phase, was considered confirmatory.

3.1. Patient disposition and populations

Of the 849 patients enrolled, 410 were randomized for the double-blind phase and 352 completed the double-blind phase of this study (Fig. 1). The ITT interim analysis set had 312 patients and the ITT final analysis set had 408 patients. Demographics and baseline characteristics were well-balanced between groups (Table 1). The mean PANSS total scores and CGI-S scores at transition phase baseline suggested that the population was symptomatically stable and at double-blind baseline indicated adequate symptom control during the maintenance phase (Table 2). The mean (SD) PSP score (for the ITT final analysis set) at transition phase baseline was 65.2 (12.08), indicating mild impairment, and at maintenance phase endpoint improved to 72.4 (10.65), indicating minimal impairment.

3.2. Treatment exposure

Approximately half the patients received either paliperidone palmitate 50 mg eq (53%) or 100 mg eq (46%) as a final dose during the transition phase. Most patients in the maintenance phase (69%) received 100 mg eq as their final dose, while 28% received 50 mg eq and 2% received 25 mg eq. Of the 205 paliperidone palmitate-assigned patients, 67% started the double-blind phase at the 100 mg eq dose. The mean (SD) dose of paliperidone palmitate was similar in the maintenance phase (82.6 [23.26] mg eq) and the double-blind phase (82.8 [24.50] mg eq). The median duration of exposure to paliperidone palmitate was 229 days (range: 6–299) in the combined transition and maintenance phases, and 171 days (range: 1–407) in the double-blind phase vs.105 days (range: 8–441) exposure to placebo for placebo-treated patients. Nearly twice as many paliperidone palmitate-assigned patients (52%) vs. placebo (28%) were exposed to study medication for approximately 6 months or longer.

Table 1
Baseline demographic characteristics (intent-to-treat analysis set).

Demographics	Interim analysis		Final analysis	
	Placebo	Paliperidone palmitate	Placebo	Paliperidone palmitate
	($n=156$)	($n=156$)	($n=203$)	($n=205$)
Age, years				
Mean (SD)	39.6 (10.78)	39.7 (11.50)	39.4 (10.77)	38.8 (11.35)
Sex, n (%)				
Men	86 (55)	86 (55)	111 (55)	109 (53)
Race, n (%)				
White	105 (67)	100 (64)	133 (66)	133 (65)
Black	28 (18)	29 (19)	36 (18)	38 (19)
Asian	21 (13)	24 (15)	30 (15)	31 (15)
Other	2 (1)	3 (2)	4 (2)	3 (1)
Body mass index[a], *kg/m²*				
Mean (SD)	27.5 (5.92)	26.9 (5.61)	27.2 (5.98)	27.3 (5.64)
Normal <25	61 (39)	63 (40)	87 (43)	78 (38)
Overweight 25 to <30	53 (34)	58 (37)	68 (33)	72 (35)
Obese ≥30	42 (27)	35 (22)	48 (24)	55 (27)

[a] Corresponds to transition baseline body mass index calculated using transition baseline weight and height.

3.3. Efficacy

3.3.1. Primary

3.3.1.1. Interim analysis. Patients randomized to continue on paliperidone palmitate during the double-blind phase experienced a significant delay in time-to-relapse compared with placebo-assigned patients ($p<0.0001$, $x^2=29.41$, Fig. 2A). Relapse event rates were significantly lower in the paliperidone palmitate group (10% of patients [$n=15/156$]), vs. placebo (34% of patients [$n=53/156$]).

3.3.1.2. Final analysis. Final analysis results for time-to-relapse were consistent with the interim analysis ($p<0.0001$, log-rank test; Fig. 2B) as were reasons for relapse. The hazard ratio (placebo/paliperidone palmitate) was 3.60 (95% CI: 2.45, 5.28). The efficacy of paliperidone palmitate with regard to time-to-relapse was consistent across all subgroups: age, BMI, sex, and geographic region.

Table 2
Psychiatric history (intent-to-treat analysis set).

Psychiatric history	Interim analysis		Final analysis	
	Placebo	Paliperidone palmitate	Placebo	Paliperidone palmitate
	($n=156$)	($n=156$)	($n=203$)	($n=205$)
Mean age at diagnosis of schizophrenia, years (SD)	27.9 (9.05)	26.5 (9.35)	28.1 (9.12)	26.4 (9.24)
PANSS total score, at transition baseline mean (SD); [range]	69.5 (16.89); [33;111]	69.3 (17.39); [32;115]	69.9 (16.97); [33;111]	69.6 (17.22); [32;115]
PANSS total score, at double-blind baseline mean (SD); [range]	53.8 (12.21); [30;83)	52.1 (12.20); [30;74]	53.1 (11.86); [30;83]	52.1 (11.81); [30;74]
CGI-S Score at transition baseline, *n* (%)				
Not ill	2 (1)	3 (2)	2 (1)	3 (1)
Very mild	19 (12)	18 (12)	25 (12)	26 (13)
Mild	54 (35)	51 (33)	66 (33)	66 (32)
Moderate	66 (42)	66 (42)	86 (42)	86 (42)
Marked	15 (10)	14 (9)	24 (12)	19 (9)
Severe	0	4 (3)	0	5 (2)
CGI-S Score at double-blind baseline, *n* (%)				
Not ill	8 (5)	9 (6)	11 (5)	11 (5)
Very mild	61 (39)	49 (31)	77 (38)	69 (34)
Mild	59 (38)	76 (49)	85 (42)	96 (47)
Moderate	28 (18)	21 (13)	30 (15)	27 (13)
Marked	0	1 (1)	0	2(1)
Previous hospitalization for psychosis, mean (SD)	2.6 (1.19)	2.5 (1.22)	2.7 (1.19)	2.6 (1.19)
Previous hospitalizations, *n* (%)				
None	15 (10)	17 (11)	21 (10)	22 (11)
Once	34 (22)	39 (25)	42 (21)	46 (22)
Two or more times	107 (69)	100 (64)	140 (69)	137 (67)

3.3.2. Secondary

Mean PANSS total scores remained relatively stable during the double-blind phase for paliperidone palmitate-assigned patients, while placebo-assigned patients showed significant worsening ($p<0.0001$) (Fig. 3). Similar results were observed for CGI-S and PSP scores (Table 3).

3.4. Safety

During the 9-week transition and 24-week maintenance phases, 67% of patients reported TEAEs (Table 4; Fig. 4A). During the variable-length double-blind phase, TEAEs that newly appeared or worsened were similar in the two groups (Table 4). Weight increase (7% paliperidone palmitate, 1% placebo) and blood glucose increase (3% paliperidone palmitate, 1% placebo) occurred more frequently (≥2% difference) in the paliperidone palmitate than the placebo group (Fig. 4B).

Serious TEAEs were mostly related to psychiatric disorder events: 11% ($n=96$) during the transition and maintenance phases (28 patients with serious TEAEs discontinued); and 12% in placebo and 4% in paliperidone palmitate treatment groups during the double-blind phase (one patient with a serious TEAE discontinued). Three deaths were reported during the transition and maintenance phases and none during the double-blind phase. Two patients additionally died post study (Table 4).

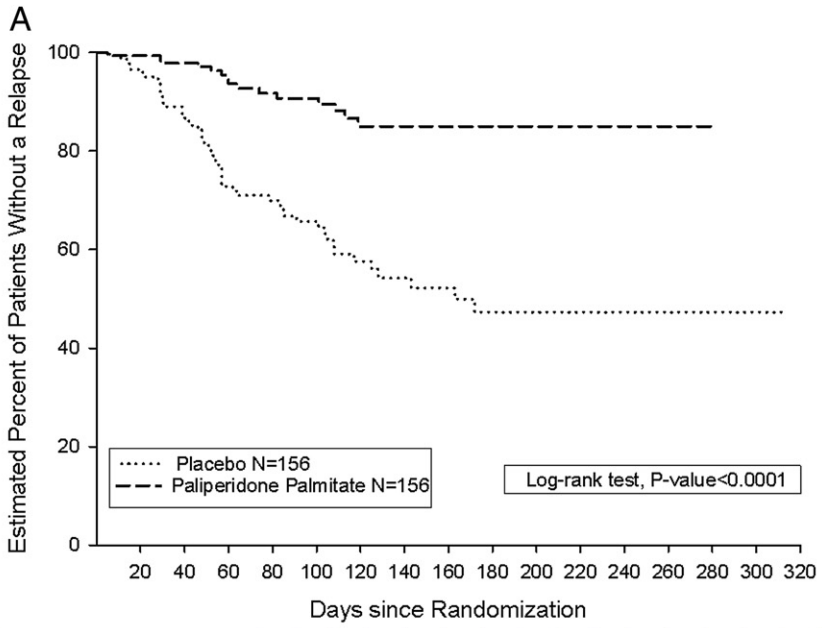
3.4.1. Other adverse events and other safety assessments of clinical interest

Mean weight from transition baseline to the double-blind endpoint increased by 1.9 kg ($n=200$ of 205) for paliperidone palmitate-assigned patients and remained unchanged for placebo patients ($n=193$ of 203). At double-blind endpoint, abnormal weight increases (≥7%) occurred in twice as many paliperidone palmitate-treated patients as placebo-treated patients from both transition baseline (23% vs. 12%) and from double-blind baseline (6% vs. 3%). The incidence of glucose-related adverse events was low (≤4%) across phases.

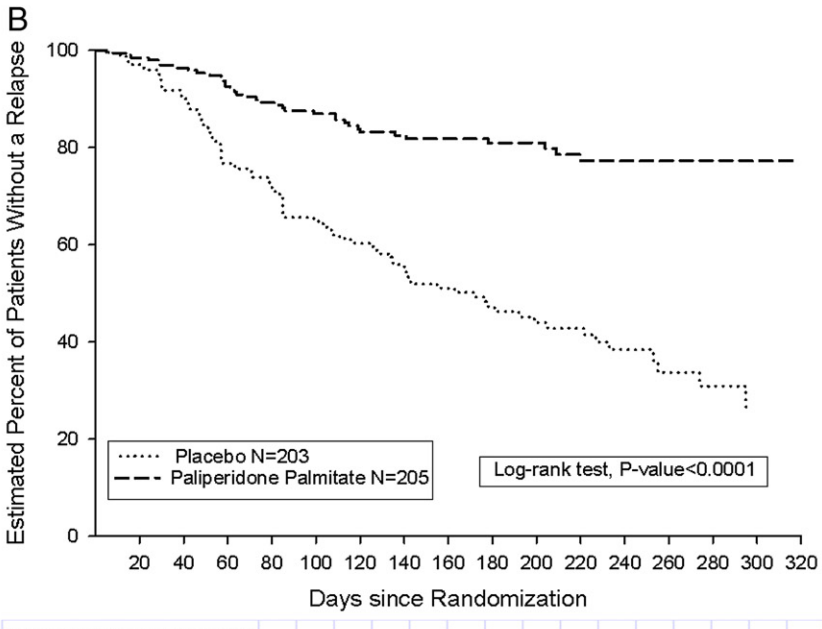
There were no clinically relevant changes from transition baseline to double-blind endpoint in EPS rating scales. EPS-related TEAEs were higher in the transition and maintenance phases (9%) compared with the double-blind phase (paliperidone palmitate: 6%; placebo: 2%). Tardive dyskinesia (mild severity) was reported in one patient during the transition phase. Anti-EPS medications were used by 12% of patients during the transition and maintenance phases and by 10% of patients on paliperidone palmitate and 6% on placebo during the double-blind phase.

There were no reports of orthostatic hypotension, ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes. Tachycardia in 9 (1%) patients (leading to discontinuation in one) and sinus tachycardia in one patient were reported only during the transition and maintenance phase. Increases in QTcLD values >480 ms were observed in two patients in the transition and maintenance phase and none during double-blind phase.

Potentially prolactin-related adverse events (AEs) were reported in 3% ($n=28$) of patients in the transition and maintenance phases, and in 2% ($n=5$) of patients on paliperidone palmitate and 1% ($n=3$) on placebo during the double-blind phase. Mean (SD) prolactin levels increased from transition baseline to maintenance phase endpoint, with greater mean increases seen in women (25.3 [45.04] ng/mL) than men (9.8 [15.83] ng/mL). During the double-blind phase, mean (SD) prolactin levels increased for the paliperidone palmitate group, again more in women (12.7 [28.64] ng/mL)



Number of Patients at Risk																	
Time	0	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320
Placebo	156	132	113	81	68	52	37	27	23	14	10	6	4	2	1	1	0
Paliperidone Palmitate	156	138	128	106	89	75	49	33	26	21	16	12	5	4	0	0	0



Number of Patients at Risk																	
Time	0	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320
Placebo	203	192	163	136	121	101	84	71	58	47	37	34	22	13	9	6	6
Paliperidone Palmitate	205	194	180	168	158	146	130	120	106	89	72	61	40	22	15	14	11

Fig. 2. Time-to-relapse. A. Intent-to-treat interim analysis set. The most common reasons for relapse were increase in the PANSS total score (placebo, $n=47$; paliperidone palmitate, $n=12$) and increase in individual PANSS item scores (placebo, $n=17$; paliperidone palmitate, $n=6$). The median time-to-relapse (the estimated time point where 50% of patients have experienced relapse) in the placebo group was 163 days, and not estimable for paliperidone palmitate: fewer than 25% of these patients experienced a relapse. The word 'risk' refers to 'risk of relapse'. At the time of interim analysis, the time-to-relapse data were censored beyond day 172 to day 313 for the placebo group and beyond day 119 to day 280 for the paliperidone palmitate group. B. Intent-to-treat final analysis set. Note—fewer paliperidone palmitate patients (18% [36/205]) than placebo patients (48% [97/203]) experienced a relapse event in the final analysis. The word 'risk' refers to 'risk of relapse'. For the final analysis, time-to-relapse data were censored beyond day 295 to day 441 for the placebo group and beyond day 220 to day 407 for the paliperidone palmitate group.

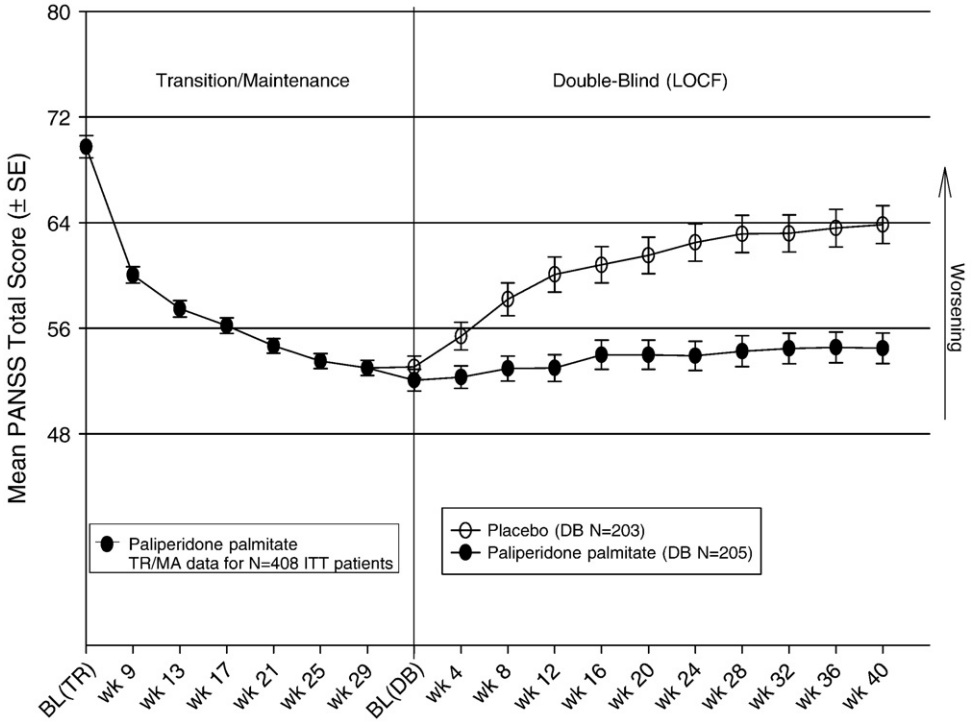


Fig. 3. PANSS total score over time (intent-to-treat final analysis set). Mean PANSS total scores are shown from baseline of the transition/maintenance phases (BL [TR]) and during these phases and then from double-blind phase (BL [DB]) baseline and during the double-blind phase. Mean PANSS total scores at double-blind baseline = 52 for paliperidone palmitate group; 53 for placebo group. PANSS = Positive and Negative Syndrome Scale; LOCF = last observation carried forward; TR = transition; MA = maintenance.

than in men (3.7[15.70] ng/mL), while mean levels decreased in the placebo group: women (−16.6 [28.70] ng/mL) and men (−9.2 [12.36] ng/mL). There were no other notable changes in most chemistry, hematology, or urinalysis laboratory parameters and vital signs from transition baseline to the end of the double-blind phase.

Local injection site tolerability was good and investigator ratings of injection site pain were similar for the placebo and paliperidone palmitate groups. Most patients reported an absence of injection site pain both during the transition and maintenance phases (76%–80%) and at double-blind endpoint (81% for paliperidone palmitate; 82% for placebo).

4. Discussion

In the current double-blind, randomized trial, treatment with the once-monthly, injectable atypical antipsychotic, paliperidone palmitate (25–100 mg eq) significantly delayed time-to-relapse of symptoms, compared with placebo, in stable patients with schizophrenia. The IDMC recommended early termination of the study as a result of the significant efficacy determined at the preplanned interim analysis. Final analysis results confirmed that once-monthly paliperidone palmitate reduced symptom severity, and maintained symptom stability. These results were generally consistent with the efficacy and safety results for the oral formulation, paliperidone ER, which was evaluated in a similarly designed trial that enrolled a comparable patient population (Kramer et al., 2007). In the current study, however, stabilized patients randomized to placebo appeared to relapse at a slower rate than those in the oral formulation study. This result could be consistent with the more gradual decline in exposure with the injectable formulation. Patients on injectable paliperidone palmitate also appeared to relapse at a slower rate than those on paliperidone ER in the oral formulation study. This might be explained by either the longer stabilization period (24 weeks) in this study vs. the paliperidone ER study (6 weeks), leading to a much longer period of clinical stability, or partial nonadherence with the oral paliperidone ER in the Kramer et al. study. This underscores the benefit of using a longer acting injectable vs. an oral antipsychotic therapy for potentially longer periods of clinical stability and to prevent partial nonadherence.

In this study, the placebo group had a nearly 4 times higher risk for relapse than the paliperidone palmitate group. The efficacy of paliperidone palmitate with regard to time-to-relapse was consistent across all subgroups assessed (age, sex, BMI, and geographic region). This risk of relapse compares favorably with the hazard ratios reported for zotepine vs. placebo in a 26-week study (Cooper et al., 2000) and quetiapine extended-release vs. placebo in a one-year study (Peuskens et al., 2008).

Although the intention of this study was to recruit both stable and symptomatic patients, the mean PANSS total scores at study entry (≤70) were consistent with a symptomatically stable population. Notably, paliperidone palmitate treatment resulted in additional improvement (approximately 20 points)

Table 3
Change in secondary efficacy measures from double-blind baseline to end of the double-blind phase (intent-to-treat final analysis set).

Efficacy measure	Placebo	Paliperidone palmitate
	($n=203$)	($n=205$)
Positive and Negative Syndrome Scale total score, mean (SD) [a]		
Baseline	53.0 (11.88)	52.0 (11.78)
Change from baseline [c]	11.1 (16.60)	2.5 (12.16) *
Clinical Global Impression-Severity Scale score, median (range) [b]		
Baseline	3.0 (1; 4)	3.0 (1; 5)
Change from baseline [c]	0 (−1; 4)	0 (−1; 3) *
Personal and Social Performance Scale score, mean (SD) [a]		
Baseline	72.9 (10.74)	72.0 (10.65)
Change from baseline [d]	−7.2 (13.03)	−1.5 (11.53) *

* $p<0.0001$ vs. placebo (least-squares mean difference).
[a] p-value based on analysis of covariance model with treatment (placebo, paliperidone palmitate) and country as factors, and baseline value as a covariate.
[b] p-value based on analysis of covariance model using ranks of change from baseline in Clinical Global Impression-Severity Scale score with treatment (placebo, paliperidone palmitate) and country as factors, and baseline value as a covariate.
[c] Decreases in scores represent improvement in the severity of neuropsychiatric symptoms.
[d] Increases in scores indicate improvement.

in the mean PANSS total score over the 33-week transition and maintenance phases for the patients in the ITT analysis set. The low mean PANSS total scores were maintained for those patients randomized to continue paliperidone palmitate treatment, whereas scores worsened for those randomized to placebo. Similarly, mean CGI-S scores improved during the transition and maintenance endpoint and were maintained during the double-blind phase in the paliperidone palmitate group.

In long-term treatment of patients with schizophrenia, a successful psychosocial integration is as important as reduction in psychopathologic symptoms (Juckel et al., 2008). The PSP is a validated and reliable tool for quickly assessing personal and social functioning of patients with schizophrenia (Juckel et al., 2008; Kawata and Revicki, 2008) and complements both the CGI-S and PANSS scales (Nasrallah et al., 2008b; Patrick et al., 2009). Subsequent to paliperidone palmitate treatment in the transition and maintenance phases, patients' mean PSP score improved by 7-points at maintenance endpoint, a clinically relevant improvement in functioning for symptomatically stable patients (Nasrallah et al., 2008b). Patients, who continued paliperidone palmitate treatment in the double-blind phase maintained this improvement, while PSP scores worsened by 7 points for placebo-treated patients.

After a period of dose optimization during the transition and maintenance periods, the discontinuation rate in the double-blind period was low (14%). This was lower than the discontinuation rates observed in previous short-term double-blind trials of both paliperidone palmitate (Nasrallah et al., 2008a; Pandina et al., submitted for publication) and risperidone long-acting therapy in symptomatic patients (Kane et al., 2003) and in a double-blind trial with paliperidone palmitate in stable patients (Hough et al., 2009), in which patients were randomized directly to fixed doses. These results may support the benefit of longer treatment trials for optimizing the dose before deciding that the patient is nonresponsive (Emsley et al., 2006).

The overall safety findings were consistent with previous short-term trials of paliperidone palmitate in symptomatic patients (Nasrallah et al., 2008a; Kramer et al., submitted for publication; Pandina et al., submitted for publication) and in a double-blind trial with paliperidone palmitate in stable patients (Hough et al., 2009). Patients treated continuously with paliperidone palmitate had a small overall mean weight gain of 1.9 kg over an average of approximately 14 months. Incidences of glucose-related adverse events were infrequent. Consistent with the known pharmacology of paliperidone, mean prolactin levels increased subsequent to paliperidone palmitate treatment, more in women than men. However, the incidence rate of prolactin-related adverse events remained low. The incidence of EPS-related adverse events (<10% across the study) was slightly higher in paliperidone palmitate-treated patients compared with placebo in the double-blind phase, consistent with previous studies (Hough et al., 2009; Nasrallah et al., 2008a; Pandina et al., submitted

Table 4
Treatment-emergent adverse events across study phases.

	Transition and maintenance (all treated patients)	Double-blind (safety patients)	
	Paliperidone palmitate	Placebo	Paliperidone palmitate
	($n=849$)	($n=203$)	($n=205$)
	n (%)	n (%)	n (%)
All TEAEs	569 (67)	91 (45)	91 (44)
Possibly related TEAE [a]	276 (33)	33 (16)	39 (19)
TEAEs leading to death [b]	3 (<1)	0	0
Death post-study [c]	2 (<1)	0	0
1 or more serious TEAE	116 (14)	26 (13)	11 (5)
TEAEs leading to discontinuation	52 (6)	1 (<1) [d]	3 (1) [e]

[a] Those considered possible, probable and very likely related to study drug.
[b] Due to suicide ($n=1$), accident, fall from window ($n=1$) and stroke ($n=1$).
[c] One patient died from accidental poisoning 19 days after discontinuation from the maintenance phase; another patient died from a 'heart attack' 10 days after discontinuation from the maintenance phase due to a suicide attempt (serious). Both deaths occurred more than 40 days after last injection of study drug.
[d] Discontinued due to a serious adverse event of myocardial infarction.
[e] One patient each discontinued to epilepsy, oculogyric crisis and weight increase.

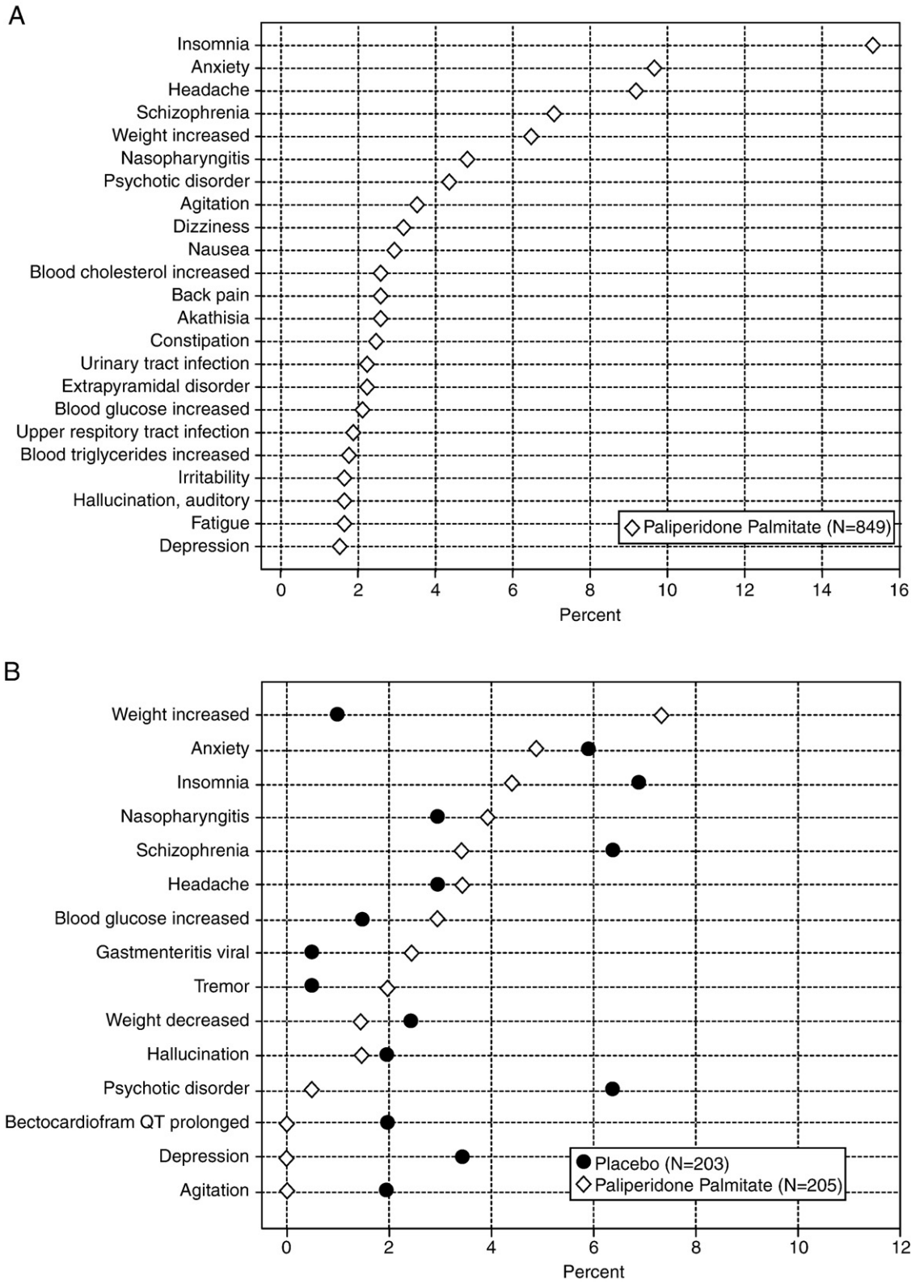


Fig. 4. Treatment-emergent adverse events experienced by at least 2% of patients in any group (safety analysis set). A. Transition and maintenance phase. B. Double-blind phase.

for publication). Injection site tolerability was good and also consistent with results from the previous paliperidone palmitate studies (Hough et al., 2009; Nasrallah et al., 2008a; Pandina et al., submitted for publication).

Any conclusions regarding optimal maintenance doses outside the range of 25–100 mg eq are limited. The use of a flexible dosing regimen mimics clinical practice. However, the general tendency of the investigator is to titrate upwards to achieve maximum efficacy. Consequently, dose reductions are rare and few were observed in this study. The extent to which the results of this study can be generalized to an adolescent or an elderly population is also limited as the study population predominantly consisted of middle-aged patients.

Paliperidone palmitate long-acting therapy, effectively reduced the symptoms of schizophrenia, improved patient functioning, and then maintained both symptom control and patient functioning, and delayed symptom relapse in patients with schizophrenia. This once-monthly, injectable formulation of paliperidone palmitate demonstrated an efficacy and tolerability profile suitable for longer-term treatment goals in patients with schizophrenia.

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Contributors

Srihari Gopal, David Hough, Mariëlle Eerdekens, Ujjwala Vijapurkar and Pilar Lim were responsible for the design and data collection for the study. Margarita Morozova was an investigator for the study, contributed data, and participated in the development of the manuscript. Ujjwala Vijapurkar and Pilar Lim were responsible for the statistical analyses. All authors critically reviewed and revised the manuscript and have approved the final manuscript.

Conflict of interest

Dr. Morozova was the principal investigator for this study and has received research support and worked as a consultant for Johnson & Johnson Pharmaceutical Research & Development, L.L.C, U.S.A.

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References

American Psychiatric Association, 1994. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition. The American Psychiatric Association, Washington, D.C, pp. 287–290.

Barnes, T.R., 1989. A rating scale for drug-induced akathisia. Br. J. Psychiatry 154, 672–676.

Cooper, S.J., Butler, A., Tweed, J., Welch, C., Raniwalla, J., 2000. Zotepine in the prevention of recurrence: A randomised, double-blind, placebo-controlled study for chronic schizophrenia. Psychopharmacology 150, 237–243.

Emsley, R., Rabinowitz, J., Medori, R., 2006. Time course for antipsychotic treatment response in first-episode schizophrenia. Am. J. Psychiatry 163, 743–745.

Guy, W. (Ed.), 1976. AIMS. Abnormal Involuntary Movement Scale, in ECDEU National Institute of Mental Health. Rockville, Md, pp. 534–537.

Hough, D., Lindenmayer, J.-P., Gopal, S., Melkote, R., Lim, P., Herben, V., Yuen, E., Eerdekens, M., 2009. Safety and tolerability of deltoid and gluteal injections of paliperidone palmitate in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 33 (6), 1022–1031.

Juckel, G., Schaub, D., Fuchs, N., Naumann, U., Uhl, I., Witthaus, H., Hargarter, L., Bierhoff, H.W., Brune, M., 2008. Validation of the personal and social performance (PSP) scale in a German sample of acutely ill patients with schizophrenia. Schizophr. Res. 104 (1–3), 287–293.

Kane, J.M., 2007. Treatment strategies to prevent relapse and encourage remission. J. Clin. Psychiatry 68 (Suppl 1), 427–430.

Kane, J.M., Eerdekens, M., Lindenmayer, J.P., Keith, S.J., Lesem, M., Karcher, K., 2003. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am. J. Psychiatry 160 (6), 1125–1132.

Kawata, A.K., Revicki, D.A., 2008. Psychometric properties of the personal and social performance scale (PSP) among individuals with schizophrenia living in the community. Qual. Life Res. 17 (10), 1247–1256.

Keith, S.J., Kane, J.M., Turner, M., Conley, R.R., Nasrallah, H.A., 2004. Academic highlights: guidelines for the use of long-acting injectable atypical antipsychotics. J. Clin. Psychiatry 65 (1), 120–131.

Kramer, M., Simpson, G., Maciulis, V., Kushner, S., Vijapurkar, U., Lim, P., Eerdekens, M., 2007. Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. J. Clin. Psychopharmacol. 27 (1), 6–14.

Kramer, M., Litman, R., Hough, D., Lane, R., Lim, P., Liu, Y., Eerdekens, M., submitted for publication. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. Intl. J. Neuropsychopharm. doi:10.1017/S1461145709990988.

Kucukalic, A., Dzubur-Kulenovic, A., Mehmedika-Suljic, E., 2007. Relapse prevention in schizophrenia—new therapeutic challenges. Psychiatr. Danub. 19 (4), 362–366.

Marder, S.R., Kramer, M., Ford, L., Eerdekens, E., Lim, P., Eerdekens, M., Lowy, A., 2007. Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomized, placebo-controlled study. Biol. Psychiatry 62, 1363–1370.

Nasrallah, H.A., Lasser, R., 2006. Improving patient outcomes in schizophrenia: achieving remission. J. Psychopharmacol. 20 (Suppl 6), 57–61.

Nasrallah, H.A., Gopal, S., Gassmann-Mayer, C., Quiroz, J.A., Lim, P., Eerdekens, M., Yuen, E., Palumbo, J., Hough, D., 2008a. Efficacy and safety of three doses of paliperidone palmitate, an investigational long-acting injectable antipsychotic in schizophrenia. Presented at American Psychiatric Association Annual Meeting, Washington DC, May 2008.

Nasrallah, H., Morosini, P., Gagnon, D.D., 2008b. Reliability, validity and ability to detect change of the personal and social performance scale in patients with stable schizophrenia. Psychiatry Res. 161 (2), 213–224.

Pandina, G., Lindenmayer, J.P., Lull, J., Lim, P., Gopal, S., Kusumakar, V., Yuen, E., Herben, V., Palumbo, J., submitted for publication. A randomized, placebo-controlled study to assess the efficacy and safety of three doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. J. Clin. Psychopharmacol.

Patrick, D.L., Burns, T., Morosini, P., Rothman, M., Gagnon, D.D., Wild, D., Adriaenssen, I., 2009. Reliability, validity and ability to detect change of the clinician-rated Personal and Social Performance scale in patients with acute symptoms of schizophrenia. Curr. Med. Res. Opin. 25 (2), 325–338.

Peuskens, J., Trivedi, J.K., Brecher, M., Svensson, O., Miller, F., Meulien, D., 2008. Long-term symptomatic remission of schizophrenia with once-daily extended release quetiapine fumarate. Schizophr. Res. 98, (Suppl.) 14–15.

Samtani, M., Gopal, S., Sliwa, J.K., Haskins, J.T., Alphs, L., Stuyckens, K., Vermeulen, A., 2009a. Switching to paliperidone palmitate from other

antipsychotics: guidance based on pharmacokinetic modeling and simulation. New Clinical Drug Evaluation Unit Meeting, June 29–July 2, Hollywood, Florida. Accessed September 28, 2009, http://208.81.106.111/Poster%20Abstract%20Book%20Final.pdf.

Samtani, M., Sliwa, J.K., Haskins, J.T., Alphs, L., Stuyckens, K., Herben, V., Vermeulen, A., 2009b. Initiation dosing of deltoid intramuscular paliperidone palmitate in schizophrenia: pharmacokinetic rationale based on modeling and simulation. J. Pharm. Pract. 22, 216–217.

Samtani, M.N., Vermeulen, A., Stuyckens, K., 2009c. Population pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia a novel once-monthly, long-acting formulation of an atypical antipsychotic. Clin. Pharmacokinet. 48 (9), 585–600.

Simpson, G.M., Angus, J.W., 1970. A rating scale for extrapyramidal side effects. Acta Psychiatr. Scand. 212, 11–19.