Tolerability of initiation doses of once-monthly paliperidone palmitate in patients with recently diagnosed schizophrenia in an acute treatment trial

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Abstract:

Objective: To examine the tolerability of the recommended initiation doses for once-monthly injectable paliperidone palmitate in patients who have recently been diagnosed with schizophrenia and for whom high doses may pose tolerability concerns.

Methods: A *post hoc* analysis from a 13-week double-blind study of patients with schizophrenia randomized 1:1:1:1 to placebo or paliperidone palmitate at 25, 100, or 150 mg equivalents (mg eq) of paliperidone (corresponding to 39, 156, or 234 mg respectively). This analysis focused on the recently diagnosed subgroup ($\leq$5 years; $N = 146$) who received the recommended initiation dosage of paliperidone palmitate [150 mg eq on day 1 ($n = 109$) followed by 100 mg eq on day 8 ($n = 39$)] or placebo ($n = 37$). Adverse events (AEs), reported in $\geq$2% of patients receiving paliperidone palmitate during days 1—7 or $\geq$5% during days 8—36, and in a higher percentage of patients receiving paliperidone palmitate than placebo, were identified. AE relative risks (RRs) and 95% confidence intervals (CIs) were determined. A RR was considered potentially significant when its 95% CI did not include 1.

Results: Overall, day 1—7 AE rates were 37.6% (41 of 109) and 29.7% (11 of 37) with paliperidone palmitate and placebo respectively; injection site pain (5.5% *versus* 2.7%, RR 2.0; 95% CI 0.25 to 16.37), agitation (4.6% *versus* 2.7%; RR 1.7; 95% CI 0.21 to 14.06), and headache (3.7% *versus* 0.0%; RR 3.1; 95% CI 0.17 to 56.41) met the $\geq$2% criteria. Day 8—36 AE rates were 41.0% (16 of 39) and 37.8% (14 of 37) with paliperidone palmitate and placebo respectively; anxiety (5.1% *versus* 0.0%; RR 4.8; 95% CI 0.24 to 95.76) met the $\geq$5% criteria.

Key limitations were that some patients may have been ill for a significant time before formal diagnosis and that the number of patients is low in this subgroup, limiting the ability to detect statistical significance for AE RRs.

Conclusions: Paliperidone palmitate initiation doses (150 mg eq day 1, 100 mg eq day 8) were tolerated in this subgroup of patients who were recently diagnosed with schizophrenia, with no unexpected findings. Although the same size was small, these data identified AEs that may be encountered during the week and month after initiation dosing. These findings may assist clinicians when paliperidone palmitate is considered an appropriate treatment choice for these patients.

Keywords: paliperidone palmitate, recent diagnosis, schizophrenia, tolerability, treatment

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Introduction

Population studies of schizophrenia have shown occurrence rates ranging from 0.1 to 0.4 per 1000 persons per year [World Health Organization, 2007; Mueser and McGurk, 2004].

Schizophrenia is a disabling and progressive disease spanning the life course from premorbid, prodromal, to deterioration and chronic or residual stages. Of these four clinical stages of schizophrenia, the emergence of frank psychosis

typically presents between the ages of 16 and 30 years with the majority of patients in the 'deterioration stage' experiencing progressive functional decline with each successive relapse [Lieberman *et al.* 2008, 2001]. The deterioration experienced by those with schizophrenia appears to be most pronounced within the first 5 years of disease onset [Tandon *et al.* 2009; Lieberman *et al.* 2001; McGlashan and Fenton, 1993; Bleuler, 1972]. Thus, it is generally accepted that the first 5–10 years of illness is a critical period for effective intervention [Francey *et al.* 2010; McGorry *et al.* 2008, 2007; Kelly *et al.* 2005; Marshall *et al.* 2005; Harrigan *et al.* 2003].

Several studies have found that earlier diagnosis and initiation of effective and well-tolerated treatment of schizophrenia is associated with greater clinical responsiveness and better long-term outcome, including a lower risk for recurrence [Weiden *et al.* 2009; Barnes *et al.* 2008; Perkins *et al.* 2005; Schooler *et al.* 2005; Wyatt, 1991], as well as possibly mitigating disease progression [Lieberman *et al.* 2001]. While patients with schizophrenia may have a robust response to treatment, those with a recent diagnosis may tolerate antipsychotic treatment less well with particular susceptibilities to extrapyramidal symptoms (EPS), weight gain, prolactin-related effects, and sedation [Salimi *et al.* 2009; Alvarez-Jimenez *et al.* 2008; Tschoner *et al.* 2007; Kelly *et al.* 2005; Llorca *et al.* 2002; Allison and Casey, 2001; Muench and Carey, 2001]. This higher sensitivity to adverse events (AEs) coupled with poor adherence to treatment are believed to be major contributors to relapse and the substantial deterioration that occurs early in the course of this chronic disease [Gilmer *et al.* 2004; Valenstein *et al.* 2004; Menzin *et al.* 2003; Coldham *et al.* 2002; Robinson *et al.* 1999]. In those at risk for poor adherence to daily therapy, the use of a long-acting injectable agent, if well tolerated, may be particularly beneficial. It has been suggested that long-acting injectable antipsychotics are a particularly appropriate treatment option in recently diagnosed patients in whom optimal therapeutic outcomes may be compromised by early treatment discontinuation and/or poor treatment adherence [Chue and Emsley, 2007; Keith and Kane, 2003]. Data from studies in patients with first episode [Kim *et al.* 2008] and recent onset psychosis [Emsley *et al.* 2008; Parellada *et al.* 2005] indicate that treatment with long-acting injectable antipsychotic agents may improve outcomes in patients with early disease symptoms.

Paliperidone palmitate is a long-acting, once-monthly (following two initiation doses given 1 week apart) injectable, atypical, antipsychotic for the treatment of adults with schizophrenia. It is the palmitate ester of paliperidone, which is also formulated for daily oral administration as paliperidone extended release (ER). The dosage of paliperidone palmitate may be expressed as milligram equivalents (mg eq) of the pharmacologically active fraction, paliperidone (Table 1).

Table 1. Corresponding dose expression equivalents of paliperidone and paliperidone palmitate.

Paliperidone (active fraction) (mg eq)	Paliperidone palmitate (mg)
150	234
100	156
75	117
50	78
25	39

The efficacy and tolerability of paliperidone palmitate for the acute and maintenance treatment of schizophrenia has been studied in several controlled clinical studies using various dosing regimens [Gopal *et al.* 2010; Hough *et al.* 2010, 2009; Nasrallah, *et al.* 2010; Pandina *et al.* 2010]. A recently completed phase 3 acute treatment trial was the first placebo-controlled study to assess paliperidone palmitate administered at the recommended day 1 dose of 150 mg eq (234 mg) by deltoid injection. Patients then received 25, 100, or 150 mg eq (39, 156, or 234 mg respectively) on day 8 and monthly thereafter (deltoid or gluteal). In this study, paliperidone palmitate was associated with significant improvements in symptomatology with no unexpected tolerability findings in adults with symptomatic schizophrenia, at all doses tested [Pandina *et al.* 2010]. A *post hoc* analysis of this trial examined the recently diagnosed subgroup to assess the effects associated with the initiation doses [150 mg eq (234 mg) on day 1 and 100 mg eq (156 mg) on day 8], which may pose a tolerability concern when managing patients early in the course of their illness.

Methods

Design

This was a *post hoc* analysis of a 13-week double-blind, randomized, placebo-controlled phase 3 acute treatment trial conducted from March 2007 to March 2008 at 72 centers in eight countries in the United States, Europe, and Asia. Adult patients with a Positive and Negative Syndrome Scale (PANSS) total score of 70–120 (inclusive) at screening and 60–120 (inclusive) at double-blind baseline were eligible for study enrollment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and consistent with Good Clinical Practices. Further details of the design are reported by Pandina and colleagues [Pandina *et al.* 2010].

Study medications

The study consisted of a screening period of up to 7 days for washout of disallowed psychotropic medications followed by a 13-week double-blind treatment period. Eligible patients were randomly assigned (1:1:1:1) to fixed doses of paliperidone palmitate 25, 100, or 150 mg eq (39, 156, or 234 mg respectively) or placebo, based on a computer-generated randomization schedule balanced by using permuted blocks of treatments and stratified by center. On day 1, all patients received a deltoid injection of paliperidone palmitate 150 mg eq (234 mg) or matching placebo; on day 8, and then on days 36 and 64, patients received their assigned treatment according to the randomization schedule, injected in the deltoid or the gluteal muscle at the discretion of the investigator. It should be noted that this differs slightly from the currently recommended initiation regimen of paliperidone palmitate that consists of 150 mg eq (234 mg) on day 1 and 100 mg eq (156 mg) on day 8, both given in the deltoid muscle, with gluteal muscle injection being an option for doses administered after day 8.

Patients were hospitalized from day 1 (first injection) until at least after the second injection of study drug on day 8. Antipsychotics, except the study drug, were prohibited during the double-blind treatment period. Antiparkinsonian medications (if EPS emerged or worsened during the study), and oral benzodiazepines (for agitation, anxiety, or sleep difficulties) at the permitted maximum daily doses, were allowed.

Tolerability and efficacy assessments

Tolerability was evaluated based on treatment-emergent AEs and related study discontinuations. Efficacy was evaluated using PANSS total scores, Clinical Global Impressions – Severity (CGI-S) ratings, and Personal and Social Performance (PSP) scores that were assessed at baseline and days 4 (PANSS and CGI-S only), 8, 22, 36, 64, and 92 (or study endpoint).

Analysis sets and statistical evaluations

All measures were assessed in the intent-to-treat (ITT) analysis set, defined as all randomized patients who took at least one dose of double-blind study medication and had both the baseline and at least one post-baseline efficacy assessment. This *post hoc* analysis of tolerability and efficacy focused on patients with 'recently diagnosed' (≤5 years) schizophrenia who received placebo or paliperidone palmitate at the recommended initiation dose of 150 mg eq on day 1 and 100 mg eq on day 8 (234 and 156 mg respectively) followed by 100 mg eq (156 mg) once monthly (days 36 and 64). This group will hereafter be referred to as the 150/100 mg eq arm. Data from the overall study population were provided as a reference where appropriate [Pandina *et al.* 2010].

Frequencies, percentages, and descriptive statistics were used to summarize demographic and clinical characteristics as well as tolerability and efficacy variables. AEs reported during days 1–7 were summarized for those reported in ≥2% of patients receiving paliperidone palmitate (included all three paliperidone palmitate treatment arms) and in a higher percentage of patients receiving paliperidone palmitate than placebo. At day 8, those assigned to paliperidone palmitate received their assigned fixed dose with approximately one-third being assigned to the 100 mg eq (156 mg) treatment arm. Because of this substantially lower total number of patients, AEs reported during days 8–36 were summarized for those reported in ≥5% of patients receiving paliperidone palmitate and in a higher percentage of patients receiving paliperidone palmitate than placebo.

Changes in weight and reports of prolactin-related and movement disorder-related events that occurred over the entire study period were summarized. AEs are presented in two panels – incidence by treatment group and relative risk (RR) with 95% confidence intervals (CIs) of an

event in the active group relative to the placebo group. A RR was considered potentially significant when its 95% CI did not include 1. For AEs with an incidence of zero in one group, a correction of 0.5 was used in the logit estimator in calculating the RR. No adjustment was made for multiplicity.

An analysis of covariance (ANCOVA) model with effects of treatment, country, and baseline value without adjustment for multiple comparisons assessed between-group changes for continuous measures. The last-observation-carried-forward (LOCF) approach was utilized. Effect sizes (treatment *versus* placebo) were calculated using Cohen's d based on the change from baseline in least-squares (LS) mean PANSS total score, mean CGI-S score, and mean PSP score at endpoint.

Results

Randomization, completion, and characteristics
Of 855 patients screened, 652 (76.3%) were randomized, and 636 (476 assigned to paliperidone palmitate and 160 to placebo) comprised the ITT overall study population analysis set. In the ITT analysis set, 146 were diagnosed within the prior 5 years and were classified as the recently diagnosed subgroup (Figure 1).

Baseline demographics and disease characteristics of the ITT recently diagnosed and overall study populations show that the recently diagnosed was a younger subgroup of the population, with a slightly later age at diagnosis, somewhat different racial distribution, but similar symptomatology (Table 2). The mean (SD) time since diagnosis in the recently diagnosed group was 2.9 (1.3) years; 38.4% ($n = 56$) were ≤2 years since diagnosis; 26.0% ($n = 38$) were >2 to 3 years since diagnosis; 20.5% ($n = 30$) were >3 to 4 years since diagnosis; and 15.1% ($n = 22$) were >4 to 5 years since diagnosis. In this group, the mean (SD) age at baseline was 31.2 (9.6) years; 34.9% ($n = 51$) were ≤25 years of age; 36.3% ($n = 53$) were >25 to 35 years of age; 28.1% ($n = 41$) were >35 to 65 years of age, and 0.7% ($n = 1$) were >65 years of age at baseline.

In the recently diagnosed subgroup, discontinuation rates due to AEs were 10.3% (4 of 39) with paliperidone palmitate 150/100 mg eq (234/156 mg) and
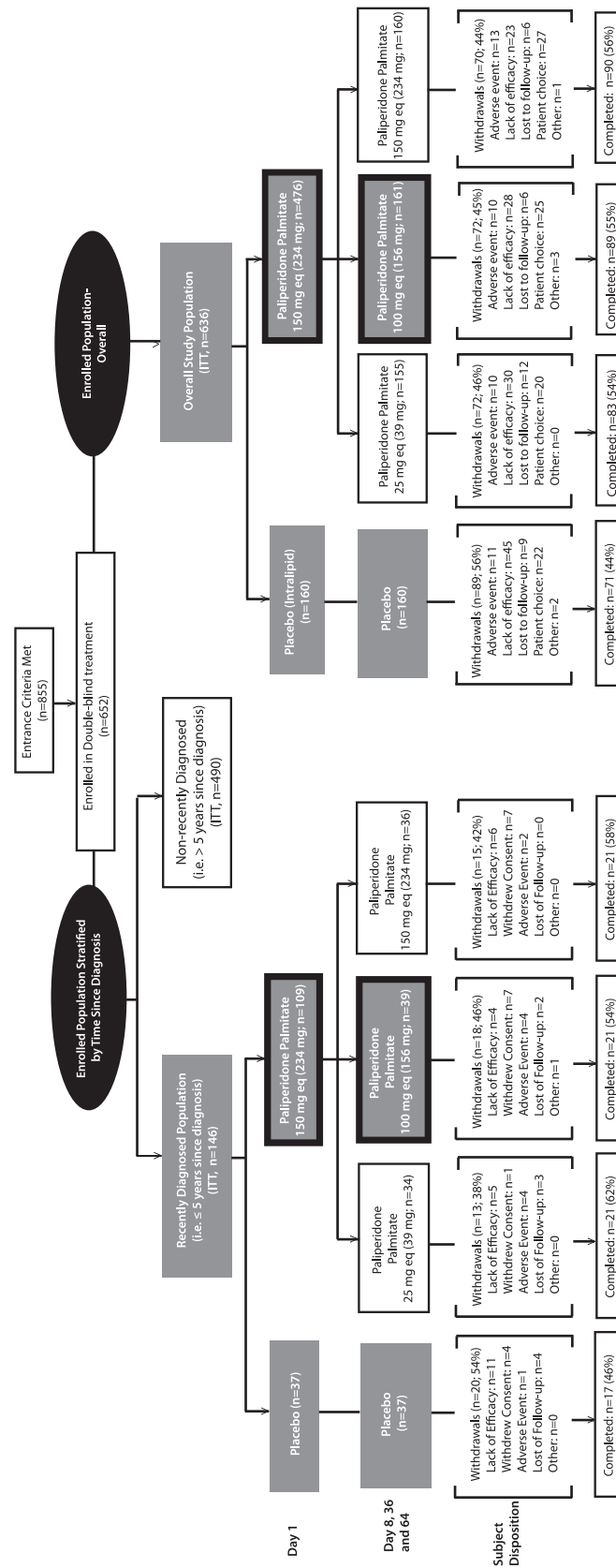
2.7% (1 of 37) with placebo. These rates in the overall study population were 6.2% (10 of 161) and 6.9% (11 of 160) respectively. AEs leading to discontinuation in the four recently diagnosed patients receiving paliperidone palmitate were: insomnia, psychotic disorder, paranoid type schizophrenia, suicidal ideation, dry mouth, toothache, injection site swelling, and musculoskeletal stiffness ($n = 1$ for each AE). AEs leading to discontinuation in the one recently diagnosed patient receiving placebo were schizophrenia and akathisia.

Tolerability during days 1–7
In the recently diagnosed subgroup, 37.6% (41 of 109) reported AEs during the week following the day 1 injection of paliperidone palmitate 150 mg eq (234 mg) and 29.7% (11 of 37) after receipt of placebo. In the overall study population, these rates were 38.0% (181 of 476) and 43.1% (69 of 160) respectively.

AEs reported by ≥2% of recently diagnosed patients receiving paliperidone palmitate and in a higher percentage of patients receiving paliperidone palmitate than placebo were injection site pain (5.5% *versus* 2.7%; RR 2.0; 95% CI 0.25 to 16.37), agitation (4.6% *versus* 2.7%; RR 1.7; 95% CI 0.21 to 14.06), and headache (3.7% *versus* 0.0%; RR 3.1; 95% CI 0.17 to 56.41) (Figure 2). RRs were not statistically significant as determined by 95% CIs. In the overall study population the same AEs met these criteria: injection site pain (paliperidone palmitate *versus* placebo 6.7% *versus* 3.8%; RR 1.8; 95% CI 0.76 to 4.21) and headache (4.0% *versus* 3.8%; RR 1.1; 95% CI 0.43 to 2.62), and agitation (3.2% *versus* 1.3%; RR 2.5; 95% CI 0.58 to 10.90). RRs were not statistically significant as determined by 95% CIs.

In the recently diagnosed subgroup, a broad range of AEs were reported in one or two patients receiving active treatment and none receiving placebo ($n = 2$ for toothache, vomiting, and myalgia; $n = 1$ for aggression, schizophrenia, dry mouth, upper abdominal pain, nausea, dizziness, exertional dizziness, lethargy, Parkinsonism, sedation, asthenia, fatigue, back pain, muscle tightness, musculoskeletal stiffness, pain in extremity, hyperhidrosis, furuncle, sialodentitis, viral infection, eye rolling, increased blood amylase, weight increase, sinus bradycardia, galactorrhea, and nasal congestion).

Figure 1. Subject randomization and completion in intent-to-treat (ITT) study populations: overall population and recently diagnosed subgroup. In the recently diagnosed subgroup, discontinuation rates due to adverse events were 10.3% (4 of 39) with paliperidone palmitate 150/100 mg eq and 2.7% (1 of 37) with placebo. Corresponding rates in the overall study population were 6.2% (10 of 161) and 6.9% (11 of 160) respectively.

Table 2. Baseline demographics of the recently diagnosed (≤5 years since diagnosis) subgroup and overall study population.

Parameter	Recently diagnosed subgroup, ITT n = 146	Overall study population, ITT n = 636
Gender, n (%)		
Male	100 (68)	427 (67)
Female	46 (32)	209 (33)
Age (years)		
Mean (SD)	31.2 (9.6)	39.4 (10.6)
Mean age at diagnosis (SD)	28.3 (9.7)	25.4 (8.2)
Race, n (%)		
Caucasian	95 (65)	343 (54)
Black	30 (21)	192 (30)
Asian	21 (14)	92 (14)
Other	0 (0)	9 (1)
Type of schizophrenia, n (%)		
Paranoid	127 (87)	558 (88)
Disorganized	1 (<1)	17 (3)
Catatonic	2 (1)	2 (<1)
Undifferentiated	14 (10)	54 (8)
Residual	2 (1)	5 (1)
PANSS total score, mean (SD)	87.3 (10.5)	87.1 (11.2)
CGI-S, n (%)	n = 146	n = 635
Mild	1 (<1)	16 (3)
Moderate	82 (56)	307 (48)
Marked	56 (38)	275 (43)
Severe	7 (5)	37 (6)

CGI-S, Clinical Global Impressions — Severity; ITT, intent to treat; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Tolerability during days 8–36

In the recently diagnosed subgroup, 41.0% (16 of 39) reported AEs in the month following the day 8 injection of paliperidone palmitate 100 mg eq (156 mg), and 37.8% (14 of 37) after placebo. In the overall study population, these rates were 38.5% (62 of 161) and 41.3% (66 of 160) respectively.

One AE, anxiety, was reported by ≥5% of recently diagnosed patients receiving paliperidone palmitate and in a higher percentage of patients receiving paliperidone palmitate than placebo (5.1% *versus* 0.0%; RR 4.8; 95% CI 0.24 to 95.76); the RR was not statistically significant (Figure 3). No AE, including anxiety (3.1% *versus* 2.5%; RR 1.2; 95% CI 0.34 to 4.54; $p > 0.05$), met the criteria in the overall study population; however, data are shown in Figure 3.

Weight, movement disorders, and prolactin during entire study

In the recently diagnosed subgroup, the LS mean (SEM) weight change over the entire study period was 1.4 kg (0.76) in the paliperidone palmitate 150/100 mg eq (234/156 mg) group and 0.0 kg (0.81) in the placebo group ($p = 0.157$ for difference in LS means). In the overall study population, the mean weight change was 0.7 kg (0.36), and −0.3 kg (0.37) respectively ($p = 0.028$ for difference in LS means).

In the recently diagnosed subgroup, movement disorder-related events were reported over the entire study period by 10.3% (4 of 39) in the paliperidone palmitate group and by 8.1% (3 of 37) in the placebo group (RR 1.3; 95% CI 0.30 to 5.27; $p > 0.05$). In the overall study population, the respective rates were: 9.3% (15 of 161) and 8.1% (13 of 160) (RR 1.2; 95% CI 0.56 to 2.33; $p > 0.05$).

In the recently diagnosed subgroup, the most common movement disorder-related event during the entire study period was Parkinsonism in the paliperidone palmitate group and hyperkinesia in the placebo group, with a similar pattern noted in the overall study population. Individual movement disorder-related event
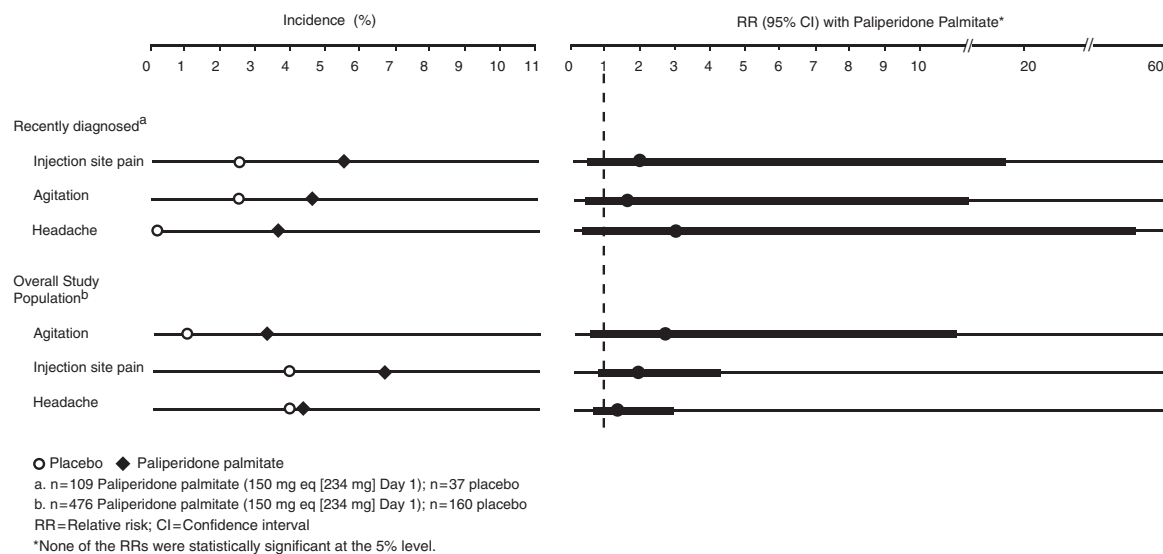
O Placebo **◆** Paliperidone palmitate
a. n=109 Paliperidone palmitate (150 mg eq [234 mg] Day 1); n=37 placebo
b. n=476 Paliperidone palmitate (150 mg eq [234 mg] Day 1); n=160 placebo
RR=Relative risk; CI=Confidence interval
*None of the RRs were statistically significant at the 5% level.

Figure 2. Days 1–7: adverse events in ≥2% of patients receiving paliperidone palmitate and in a higher percentage of patients receiving paliperidone palmitate than placebo. Events that met these criteria during the week following the first injection in the recently diagnosed subgroup were injection site pain, agitation, and headache; relative risks were not statistically significant as determined by the 95% confidence intervals. The same events met these criteria in the overall study population.
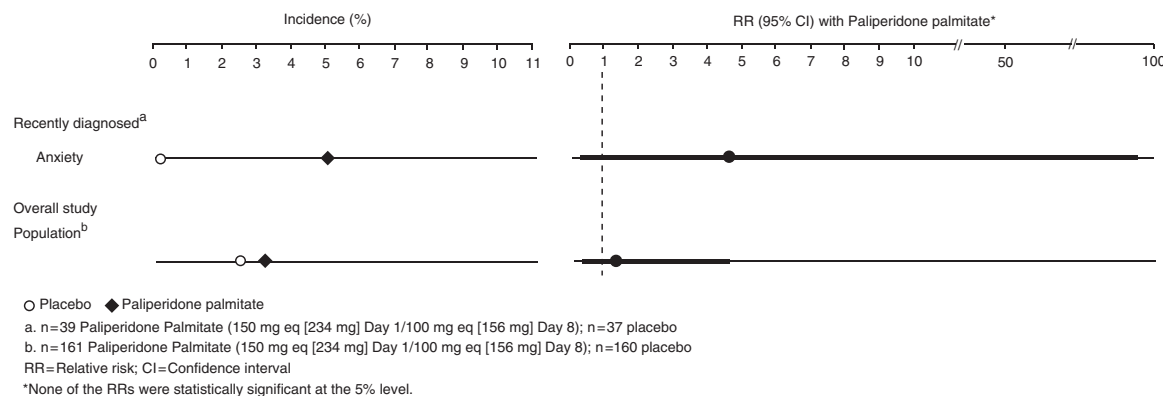

O Placebo **◆** Paliperidone palmitate
a. n=39 Paliperidone Palmitate (150 mg eq [234 mg] Day 1/100 mg eq [156 mg] Day 8); n=37 placebo
b. n=161 Paliperidone Palmitate (150 mg eq [234 mg] Day 1/100 mg eq [156 mg] Day 8); n=160 placebo
RR=Relative risk; CI=Confidence interval
*None of the RRs were statistically significant at the 5% level.

Figure 3. Days 8–36: adverse events in ≥5% of patients receiving paliperidone palmitate and in a higher percentage of patients receiving paliperidone palmitate than placebo. In the recently diagnosed subgroup, anxiety met the criteria during the first month following the second injection; the relative risk was not statistically significant as determined by the 95% confidence interval. No events met these criteria in the overall study population.

incidence rates and RRs with 95% CIs that occurred during the study are illustrated in Figure 4. The RRs were not statistically significant as determined by the 95% CIs.

In the recently diagnosed subgroup, one male placebo-treated patient reported ejaculation disorder. In the overall study population, there was an additional report of one female patient in the paliperidone palmitate group who reported loss of libido (Figure 5).

Efficacy during entire study
There was a significant improvement from baseline in PANSS total score at endpoint in recently diagnosed patients who received paliperidone
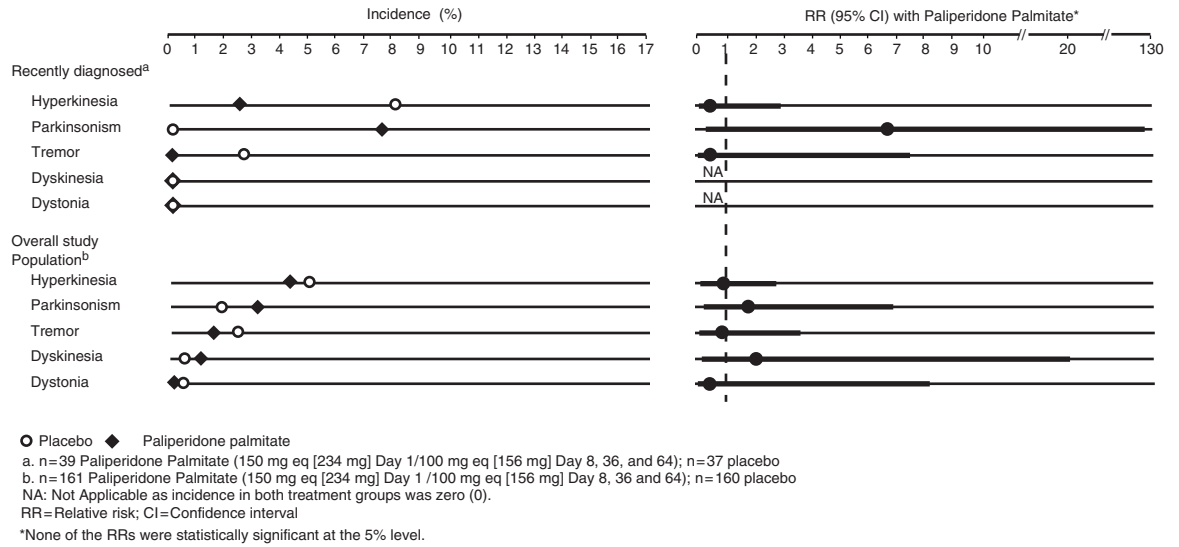
Incidence (%)

RR (95% CI) with Paliperidone Palmitate*

O Placebo ◆ Paliperidone palmitate
a. n=39 Paliperidone Palmitate (150 mg eq [234 mg] Day 1/100 mg eq [156 mg] Day 8, 36, and 64); n=37 placebo
b. n=161 Paliperidone Palmitate (150 mg eq [234 mg] Day 1 /100 mg eq [156 mg] Day 8, 36 and 64); n=160 placebo
NA: Not Applicable as incidence in both treatment groups was zero (0).
RR=Relative risk; CI=Confidence interval
*None of the RRs were statistically significant at the 5% level.

Figure 4. Movement disorder-related adverse events over entire study. Parkinsonism was the most common movement disorder-related event during the entire study period in the recently diagnosed subgroup given paliperidone palmitate, with hyperkinesia being the most common movement disorder-related event in those given placebo. As with other events, the relative risks were not statistically significant as determined by the 95% confidence intervals.
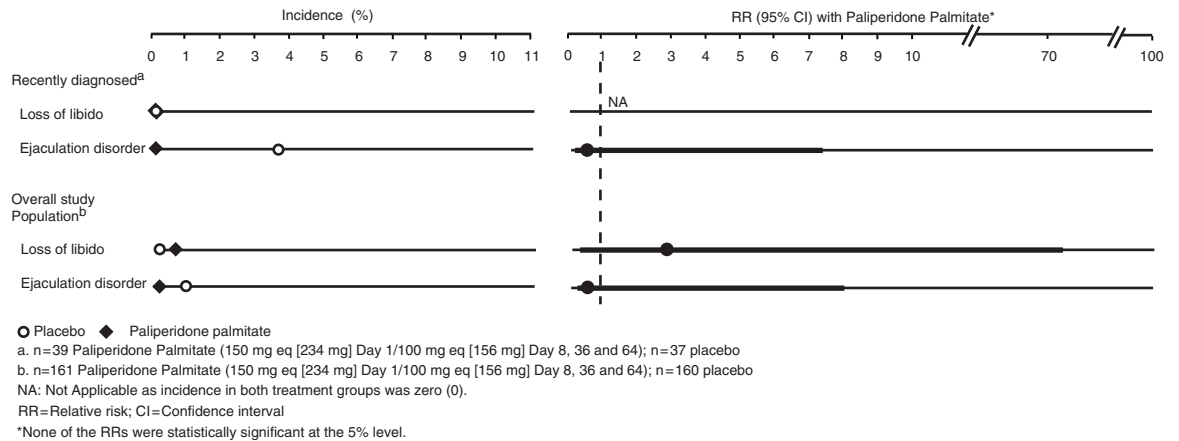

Incidence (%)

RR (95% CI) with Paliperidone Palmitate*

O Placebo ◆ Paliperidone palmitate
a. n=39 Paliperidone Palmitate (150 mg eq [234 mg] Day 1/100 mg eq [156 mg] Day 8, 36 and 64); n=37 placebo
b. n=161 Paliperidone Palmitate (150 mg eq [234 mg] Day 1/100 mg eq [156 mg] Day 8, 36 and 64); n=160 placebo
NA: Not Applicable as incidence in both treatment groups was zero (0).
RR=Relative risk; CI=Confidence interval
*None of the RRs were statistically significant at the 5% level.

Figure 5. Prolactin-related adverse events over entire study. One male patient with recently diagnosed schizophrenia treated with placebo reported ejaculation disorder during the entire study period. In the overall study population, there was one additional report of a female patient treated with paliperidone palmitate who reported a loss of libido.

palmitate 150/100 mg eq (234/156 mg) compared with those who received placebo (Table 3). The effect size (*versus* placebo) based on the LS mean score change was −0.7 (95% CI −1.16 to −0.23; $p = 0.0031$) in the recently diagnosed subgroup; it was −0.5 (95% CI −0.69 to −0.25; $p < 0.0001$) in the overall study population.

In the recently diagnosed subgroup, effect sizes for improvements in CGI-S and PSP with paliperidone palmitate compared with placebo were similar to those observed in the overall study population, but they were not statistically significant in this subgroup (Table 3). In the overall study population (with much larger

Table 3. PANSS, CGI-S, and PSP mean baseline, mean changes from baseline to endpoint and effect sizes: paliperidone palmitate *versus* placebo (95% confidence interval, *p*-value).

Parameter	Recently diagnosed subgroup		Overall study population	
	Paliperidone palmitate 150/100 mg eq (234/156 mg) (n = 39)	Placebo (n = 37)	Paliperidone palmitate 150/100 mg eq (234/156 mg) (n = 161)	Placebo (n = 160)
PANSS total				
Baseline, mean (SD)	88.1 (10.89)	85.2 (10.39)	86.2 (10.77)	86.8 (10.31)
Change from baseline at endpoint, mean (SD)	−16.5 (20.43)	−2.2 (20.91)	−11.6 (17.63)	−2.9 (19.26)
Effect size at endpoint	−0.7 (−1.16, −0.23) *p* = 0.0031		−0.5 (−0.69, −0.25) *p* < 0.0001	
CGI-S score				
Baseline, mean (SD)	4.4 (0.60)	4.4 (0.65)	4.4 (0.63)	4.6 (0.63)
Change from baseline at endpoint, mean (SD)	−0.8 (1.21)	−0.3 (1.29)	−0.6 (1.13)	−0.3 (1.13)
Effect size at endpoint	−0.4 (−0.88, 0.03) *p* = 0.0675		−0.3 (−0.48, −0.04) *p* = 0.0192	
PSP total				
Baseline, mean (SD)	49.9 (12.40)	51.4 (11.84)	50.2 (12.78)	49.7 (12.33)
Change from baseline at endpoint, mean (SD)	9.2 (13.68)	2.9 (17.46)	6.1 (13.59)	1.7 (15.60)
Effect size at endpoint	0.4 (−0.05, 0.86) *p* = 0.835		0.3 (0.08, 0.52) *p* = 0.0085	

Effect size at endpoint was for paliperidone palmitate versus placebo. The type of effect size is Cohen's d; *p*-value is from two-sided *Z* test. CGI-S, Clinical Global Impressions — Severity; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; SD, standard deviation.

sample sizes), these effect sizes were statistically significant.

Discussion

The primary objective of this subgroup analysis was to assess the tolerability associated with the initiation doses of paliperidone palmitate in this potentially sensitive patient population. The recommended initiation dosing for paliperidone palmitate requires use of the higher doses given 1 week apart (150 mg eq on day 1 and 100 mg eq on day 8; 234 and 156 mg respectively) in the deltoid muscle, and is followed by once-monthly injections of 25–150 mg eq (39–234 mg). Published data show lower initial doses administered in the gluteal muscle can lead to subtherapeutic plasma levels and poor longer-term response in schizophrenia [Gopal *et al.* 2010; Nasrallah *et al.* 2010]. Nonetheless, the recommended initial dosing may raise tolerability concerns for clinicians, particularly when managing patients early in the course of their illness where relatively low doses of antipsychotics are commonly preferred [McGorry and Group IEPAW, 2005; Schooler *et al.* 2005]. Thus, data presented here examined this issue.

In this analysis, paliperidone palmitate at 150 mg eq on day 1 and 100 mg eq on day 8 (234 and 156 mg respectively) was tolerated without any new or unexpected AEs in patients recently diagnosed with schizophrenia. However, during the week following the initial injection of 150 mg eq (234 mg) paliperidone palmitate, the total AE rate was higher compared with the rate observed with placebo (37.6% *versus* 29.7%). This differed from that in the overall study population (38.0% and 43.1%, respectively).

Of note, the differential in the total AE rate during the first week was due to a lower rate in the placebo arm of the recently diagnosed subgroup. While there is not an obvious interpretation of this placebo arm observation, in general the data do suggest that the recently diagnosed represent a subgroup likely to report AEs with active treatment. Further, discontinuations due to AEs occurred in four of 39 patients in the paliperidone palmitate group and one of 37 in the placebo group. These findings are consistent with the significant body of literature showing that patients with schizophrenia are more sensitive to adverse drug effects in the first few years of illness [Francey *et al.* 2010; Alvarez-Jimenez *et al.* 2008; Tschoner *et al.* 2007; Kelly *et al.* 2005; Llorca *et al.* 2002; Allison and Casey, 2001; Muench and Carey, 2001]. Specifically, published reports suggest that various EPS, weight gain, prolactin-related effects, and sedation are more frequent and problematic in patients with early illness [Kelly *et al.* 2005; Bobes *et al.* 2003; Merlo *et al.* 2002; Woods *et al.* 2002; Gupta *et al.* 2001; Masi *et al.* 2001; Sanger *et al.* 1999; Wudarsky *et al.* 1999]. In our dataset, the most common events during the first week were injection site pain, agitation, and headache in both the recently diagnosed subgroup as well as the overall study population, with similar RRs. Therefore, the most commonly reported AEs with paliperidone palmitate were not those that led to the higher rate of total events with treatment in the recently diagnosed. Further, no specific AE or class of AEs was identified as a particular concern in this subgroup after the initial injection of 150 mg eq (234 mg) paliperidone palmitate. Instead, there was a broad range of events reported in one or two patients with active treatment and in no patients receiving placebo, contributing to the higher observed rate.

During the month following the day 8 injection of 100 mg eq (156 mg), the total AE rate was somewhat comparable with paliperidone palmitate and placebo in the recently diagnosed subgroup (41.0% and 37.8%), and similar to that observed in the overall study population (38.5% and 41.3%). Thus, the higher rate of total AEs noted in the first week with active treatment did not appear to continue during the following month.

As stated above, EPS, weight gain, prolactin-related effects, and sedation have been identified as areas of concern with antipsychotic treatment in early illness patients. Further, it is relevant to note that these tolerability issues have also been associated with nonadherence, a particular concern in these patients [Kelly *et al.* 2005]. Since related AE rates were low in this dataset, they were further examined over the entire study period (*versus* just the first 36 days). Among the specific types of EPS, Parkinsonism was the most commonly reported in the recently diagnosed patients receiving paliperidone palmitate 150/100 mg eq (234/156 mg), and hyperkinesia in those receiving placebo. The literature is somewhat mixed on which types of EPS the early illness patients are likely to experience, with reports suggesting akathisia, dystonia, and Parkinsonism [Kelly *et al.* 2005; Janno *et al.* 2004; Seretti *et al.* 2004; Kasper, 1999]. Hence, the Parkinsonism finding was not unexpected for these patients, and consistent with the known tolerability profile for the paliperidone molecule [Canuso *et al.* 2010; Nasrallah *et al.* 2010; Pandina *et al.* 2010; Hough *et al.* 2009; Davidson *et al.* 2007; Kane *et al.* 2007; Kramer *et al.* 2007; Marder *et al.* 2007]. Further, the RR for anxiety was 4.8 (95% CI 0.24 to 95.76) in the recently diagnosed subgroup during the month after the day 8 initiation dose. Importantly, it cannot be ruled out that some reports of anxiety may actually be associated with akathisia. Thus, the reports of Parkinsonism, and possibly anxiety, in this subgroup analysis may raise the consideration of using lower initiation doses or lower subsequent monthly doses in patients with recently diagnosed schizophrenia. Relevant to this issue, it is important to note that lower initiation doses of paliperidone palmitate have been associated with subtherapeutic plasma levels [Gopal *et al.* 2010]. Further, this study was designed so that patients who received the recommended initiation doses of paliperidone palmitate then received 100 mg eq (156 mg) monthly dosing during the 13-week trial. However, since subsequent monthly dosing with paliperidone palmitate may range from 25 to 150 mg eq (39–234 mg), doses lower than 100 mg eq (156 mg) may be appropriate for some patients.

There were few reports of potentially prolactin-related effects in this dataset, and none reported in more patients receiving active treatment than placebo, except for the one report of galactorrhea in the paliperidone palmitate group compared with none in the placebo group. Also, the data on weight (mean weight gain and reports of weight gain) and sedation, observed in this

dataset, did not suggest a substantial susceptibility in the recently diagnosed subgroup compared with the overall study population during this 13-week study period.

The original study was not designed to answer the question posed here, and as such, several limitations must be considered. First, it is important to note that this was a subgroup analysis, and the low number of patients limited the ability to identify, differentiate, or make conclusions regarding the risk of infrequent or rare AEs. Second, the 5-year cutoff as a definition for a recent diagnosis relied on historical information which may not be accurate, and many patients are ill for a significant period of time before receiving a formal diagnosis. In fact, identifying the onset of schizophrenia is often challenging because of the range of defining events [Tandon *et al.* 2009]. Nonetheless, it is generally accepted that the first 5–10 years of illness is a critical period for effective intervention [Francey *et al.* 2010; McGorry *et al.* 2008, 2007; Kelly *et al.* 2005; Marshall *et al.* 2005; Harrigan *et al.* 2003]. The 5-year cutoff used here should have captured a population enriched for this stage of the illness. However, a first episode population may have shown a greater level of intolerance.

Of note, the data presented here focused on the first 36 days of treatment to examine the tolerability specifically associated with the initiation doses of paliperidone palmitate (150 mg eq on day 1 and 100 mg eq on day 8; 234 and 156 mg respectively) in this sensitive patient population. It is important to remember that this study protocol permitted clinicians to administer the second initiation dose in either the gluteal or deltoid muscle, which differs somewhat from the recommended regimen that both initiation doses be administered in the deltoid muscle. In addition, longer-term tolerability is an important issue which could not be addressed in this 13-week study. Longer-term data have been reported elsewhere for broader patient populations [Hough *et al.* 2009], and an initial analysis was reported for those recently diagnosed [Alphs *et al.* 2009].

In this dataset, measures of symptomatology suggest that the recently diagnosed subgroup is quite responsive to treatment with paliperidone palmitate, without oral supplementation. The PANSS effect sizes for treatment *versus* placebo were similar in this subgroup to those observed in the overall study population, although they did not reach statistical significance in the former group for CGI and PSP (partly because of the small number of patients). The responsiveness of symptoms to treatment has been published in reports regarding first-episode patients [Ucok *et al.* 2004; Robinson *et al.* 1999]. Our finding confirms that tolerability with medications, not lack of efficacy, is an area of primary concern when managing these patients with early illness.

Current knowledge suggests that early detection and a shorter duration of untreated psychosis are key factors to optimizing outcome in patients with schizophrenia [Francey *et al.* 2010; Ucok *et al.* 2004; McGlashan *et al.* 2001; Falloon *et al.* 1996]. Thus, early comprehensive psychosocial interventions and antipsychotic medications, when clinically indicated, are typical standards of care for these patients [Francey *et al.* 2010; Kelly *et al.* 2005; Lieberman et al 2001]. While challenges to this dogma of early antipsychotic use have been raised [Francey *et al.* 2010], treatment is generally required for many patients with early illness and evident psychosis. While these patients are often responsive to the efficacy benefits of pharmacological agents, tolerability and adherence to treatment remain key areas of concern [Kelly *et al.* 2005; Fleischhacker *et al.* 1994]. Although none of the AEs identified in the first 36 days after initiating paliperidone palmitate treatment had a statistically significant RR as determined by 95% CIs, the small number of patients limited our ability to detect significance. Nonetheless, these data do identify AEs that clinicians may encounter when managing these patients. Thus, the findings presented here may help guide clinicians when paliperidone palmitate is considered an appropriate treatment of choice for these patients.

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Conflicts of interest statement

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