Neuropsychiatric Disease and Treatment

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Paliperidone palmitate and risperidone long-acting injectable in subjects with schizophrenia recently treated with oral risperidone or other oral antipsychotics

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
4 March 2013
Number of times this article has been viewed

Larry Alphs[1]
Cynthia A Bossie[1]
Jennifer Kern Sliwa[2]
Dong-Jing Fu[1]
Yi-Wen Ma[3]
Joseph Hulihan[1]

[1]CNS Medical Affairs, [2]Medical Information, Janssen Scientific Affairs, LLC, Titusville, NJ, USA; [3]Biostatistics, B&P, Janssen Research & Development LLC, Titusville, NJ, USA

Background: This post hoc subgroup analysis of a randomized, double-blind trial evaluated the response to treatment with two long-acting injectable atypical antipsychotics, ie, paliperidone palmitate and risperidone long-acting injectable (RLAI), in subjects with schizophrenia experiencing clinically significant symptoms despite recent treatment with oral risperidone only or other oral antipsychotics.

Methods: Adult subjects were eligible for the 13-week, double-blind, double-dummy trial (NCT00589914) if they had an established diagnosis of schizophrenia for at least one year and a Positive and Negative Syndrome Scale (PANSS) total score of 60–120 inclusive at screening. Subjects received either paliperidone palmitate (234 mg, day 1; 156 mg, day 8; then once-monthly flexible dosing) or RLAI (25–50 mg biweekly, with oral risperidone supplementation on days 1–28), plus matched placebo injections/tablets.

Results: This post hoc analysis reports data on 747 subjects who, within 2 weeks of starting double-blind study medication, had reportedly received oral risperidone only (paliperidone palmitate group, n = 126; RLAI group, n = 107), other oral antipsychotics (paliperidone palmitate group, n = 199; RLAI group, n = 203), or no antipsychotic (paliperidone palmitate group, n = 56; RLAI group, n = 56). Mean PANSS total scores improved significantly at end point across all subgroups (mean change from baseline ranged from −17.5 to −19.5, all $P < 0.0001$). Clinical Global Impression-Severity and Personal and Social Performance scale measures also significantly improved from baseline (all $P < 0.0001$).

Conclusion: Treatment with paliperidone palmitate or RLAI resulted in a significant reduction in the symptoms of schizophrenia irrespective of previous recent treatment with oral risperidone only or other oral antipsychotics. For subjects who had previously received oral risperidone only, the difference in formulation was the main change in the intervention because the molecule delivered remained the same or similar. These data support the contribution of a long-acting formulation to improving the treatment response and suggest that nonadherence may be a significant contributor to inadequate efficacy of oral formulations in subjects with schizophrenia.

Keywords: paliperidone palmitate, risperidone long-acting injection, schizophrenia

Video abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use: http://dvpr.es/TWSfso

Correspondence: Larry Alphs
Janssen Scientific Affairs LLC,
1125 Trenton-Harbourton Road
A32404, Titusville, NJ 08560, USA
Tel +1 609 730 3693
Fax +1 609 730 3125
Email lalphs@its.jnj.com

Introduction

Treatment options tailored to patient and clinician choice are an important aspect of therapy for schizophrenia. Unfortunately, adherence to treatment with oral antipsychotics is poor,[1] and this is associated with clinical and functional deterioration, increased risk of relapse, rehospitalization, and increased risk for suicidal behavior.[2–5]

Simplified antipsychotic regimens that can provide continuous long-term symptom relief may be helpful in improving these outcomes. In this regard, long-acting injectable antipsychotics may improve adherence over oral antipsychotics by reducing the requirement from daily dosing to biweekly or monthly dosing.[3,6–9] This reduces the requirement for patients to remember to take their medication from 365 times annually for once-daily oral dosing, to 26 times annually for biweekly dosing or 12 times annually for monthly dosing. Further, health care providers can be certain of their patients' level of adherence to their medications, and resources are not wasted on medication that is discarded or forgotten.

Paliperidone palmitate and risperidone long-acting injection (RLAI) are two long-acting, injectable, atypical antipsychotics that are effective in treating schizophrenia.[10–15] They deliver related molecules (paliperidone [9-hydroxy risperidone] and risperidone, respectively) using formulations with different pharmacologic and release profiles and different initiation and maintenance regimens. Paliperidone palmitate is the palmitate ester of paliperidone.[16–18] Treatment with paliperidone palmitate is initiated with deltoid injections (234 mg on day 1 and 156 mg on day 8), followed by once-monthly injections (deltoid or gluteal, 39–234 mg), without oral supplementation.[19] RLAI is a microsphere formulation of risperidone and is administered intramuscularly biweekly (25–50 mg).[20] Because less than 1% of risperidone is released during the first 3 weeks of treatment with RLAI, oral supplementation with risperidone (or another antipsychotic) should accompany the first RLAI dose and continue for the initial 3 weeks of RLAI treatment.[20]

Until novel therapies are developed that offer new mechanisms of action for treating schizophrenia, improving delivery of effective agents and addressing the problem of daily adherence remain important strategies to improve outcomes for these individuals. However, because of the pharmacologic relationships between risperidone and paliperidone palmitate and among the active entities of their oral and injectable formulations, questions may be raised about the efficacy of RLAI and paliperidone palmitate in subjects who have recently been treated with oral risperidone but continue to experience symptoms of schizophrenia. This post hoc analysis was undertaken to compare treatment responses to RLAI and paliperidone palmitate in subjects who had recently been treated with oral risperidone only, who had been treated with other antipsychotics, or who were not receiving any antipsychotic treatment at the time they entered the study. These exploratory findings are informative about whether the long-acting formulations of these agents offer benefit to subjects with persistent symptoms despite recent antipsychotic therapy with an oral version of the same or a similar product.

Materials and methods

Study design

This was a post hoc analysis of a 13-week, double-blind, double-dummy, multicenter study (NCT00589914). The original study was designed to evaluate the efficacy and safety of paliperidone palmitate treatment as compared with RLAI in adult subjects with schizophrenia and demonstrated the noninferiority of paliperidone palmitate versus RLAI in the primary efficacy variable in subjects with schizophrenia; details of the original study population and results of the noninferiority analysis are published elsewhere.[21] This post hoc analysis was performed to assess the efficacy of a long-acting injectable antipsychotic (either paliperidone palmitate or RLAI) in those subjects from the original trial who had been treated within 2 weeks before starting double-blind study medication with oral risperidone only or with other antipsychotics. Subjects who were not taking oral antipsychotics immediately prior to the trial were also included in the analysis. Previous long-acting injectable antipsychotic treatment was not part of this subgroup analysis because the original study excluded subjects who had received an injectable antipsychotic within one injection interval before screening. Subjects who had received oral paliperidone previously were excluded because the sample size was too small (n = 18).

Subjects

Adult men and women aged ≥18 years were eligible for the original study if they had met *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision,*[22] criteria for schizophrenia for at least one year; had a screening Positive and Negative Syndrome Scale (PANSS)[23] total score between 60 and 120, inclusive; and had a body mass index of 17–40 kg/m^2, inclusive. All subjects provided written informed consent before study entry, and the original study protocol was reviewed by an independent ethics committee or an institutional review board at each study site. The trial was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practices and applicable regulatory requirements.

Study medication

Subjects were randomly assigned in a 1:1 ratio to receive paliperidone palmitate or RLAI. Paliperidone palmitate was

administered via deltoid injection on day 1 (234 mg) and again on day 8 (156 mg), followed by once-monthly deltoid or gluteal injections according to subject choice on days 36 (78 or 156 mg) and 64 (78, 156, or 234 mg), with RLAI-matched placebo gluteal injections. RLAI was administered as biweekly gluteal injections at day 8 (25 mg), then day 22 (25 mg), days 36 and 50 (25 or 37.5 mg), and days 64 and 78 (25, 37.5, or 50 mg), with paliperidone palmitate–matched placebo deltoid or gluteal injections. RLAI subjects received oral risperidone supplementation (1–6 mg/day, days 1–28; optional thereafter with dose increases); paliperidone palmitate subjects received oral placebo. Where flexible doses of medication were permitted, the choice was determined by the treating physician based on perceived risk versus benefit.

Paliperidone palmitate doses may also be expressed as milligram equivalents (mg eq) of paliperidone, with 39, 78, 117, 156, and 234 mg of paliperidone palmitate being equivalent to 25, 50, 75, 100, and 150 mg eq of paliperidone, respectively.[16,19] This report expresses paliperidone palmitate as milligrams.

Concomitant medication

Subjects were allowed to continue receiving antidepressants (except for nonselective and irreversible monoamine oxidase inhibitors) if they had been on a stable dose for at least 30 days before screening. Antiparkinsonian medication was washed out before study entry but could be reintroduced by the investigator if extrapyramidal symptoms emerged or worsened during the study; allowed antiparkinsonian medications were trihexyphenidyl, benztropine, biperiden, and antihistamines with anticholinergic properties. Oral benzodiazepines (at permitted maximum daily doses) were also allowed, preferably lorazepam. Mood stabilizers (including lithium and all anticonvulsants) and any prescription, herbal, or over-the-counter agents with psychotropic actions were not allowed during the double-blind treatment period.

Study assessments

Assessments included change from baseline to end point in PANSS total, PANSS factors,[24] Clinical Global Impression–Severity (CGI-S),[25] and Personal and Social Performance (PSP)[26] scale scores. Responder rate (defined as those subjects with a 30% or greater improvement in PANSS total score from baseline) was also determined. Adverse event reports were collected at each visit from the time an informed consent form was obtained until completion of the last study-related procedure.

Statistical analysis

For this post hoc subgroup analysis, data were analyzed separately for the paliperidone palmitate and RLAI subpopulations. There was no statistical comparison between the two treatment arms of the study because subjects had not been randomly assigned within the subgroups, and this was not the objective of the analysis. For the initial analysis of the overall study, four analysis sets were defined, ie, the safety analysis set, the intent-to-treat analysis set, the per-protocol analysis set, and the pharmacokinetic analysis set.[21] For this post hoc subgroup comparison, the per-protocol analysis set, originally used only for the primary efficacy analysis,[21] was considered appropriate for analysis of all efficacy and safety assessments as the comparison was exploratory and did not look at early time points. The per-protocol set was defined as all subjects with a baseline and at least one post randomization PANSS measure, minimum exposure of 36 days to the double-blind treatment regimen, and no major protocol violations.[21] Within each treatment group, subjects were analyzed based on whether they had received oral risperidone treatment only, treatment with another antipsychotic, or no previous antipsychotic treatment in the 2 weeks before starting double-blind study medication. Mean (±standard deviation), median, minimum, and maximum were used for summary of continuous variables; percentage and frequency were used for categorical variables. Within-group differences were evaluated using a paired *t*-test. All statistical tests were two-sided, and no adjustments were made for multiplicity. The analysis used last-observation-carried-forward methodology.

Results

Subject disposition, baseline demographics, and clinical characteristics

A total of 747 subjects (61% of those randomized) from the original study were included for this subgroup analysis (Table 1). Two hundred thirty-three subjects received oral risperidone only within 2 weeks before starting double-blind study medication (paliperidone palmitate treatment arm, n = 126; RLAI treatment arm, n = 107). A further 402 subjects had received some other oral antipsychotic within 2 weeks before starting double-blind study medication (paliperidone palmitate, n = 199; RLAI, n = 203), and 112 subjects were not receiving any antipsychotics during the 2 weeks before starting double-blind study medication (n = 56 for both study arms).

Table 1 Baseline demographics and clinical characteristics

	Paliperidone palmitate			RLAI		
	Prior Ris only (n = 126)	Prior other AP[a] (n = 199)	No prior AP (n = 56)	Prior Ris only (n = 107)	Prior other AP[a] (n = 203)	No prior AP (n = 56)
Age, years, mean (SD)	38.8 (11.5)	40.2 (11.5)	39.0 (11.8)	38.4 (11.0)	39.4 (12.6)	37.9 (10.9)
Gender, n (%)						
Male	77 (61.1)	104 (52.3)	41 (73.2)	56 (52.3)	110 (54.2)	28 (50.0)
Female	49 (38.9)	95 (47.7)	15 (26.8)	51 (47.7)	93 (45.8)	28 (50.0)
Race, n (%)						
Caucasian	109 (86.5)	158 (79.4)	41 (73.2)	95 (88.8)	161 (79.3)	43 (76.8)
African American	12 (9.5)	20 (10.1)	10 (17.9)	6 (5.6)	22 (10.8)	10 (17.9)
Asian	5 (4.0)	20 (10.1)	5 (8.9)	6 (5.6)	20 (9.9)	1 (1.8)
Other	0	1 (0.5)	0	0	0	2 (3.6)
Age at diagnosis, years, mean (SD)	28.3 (8.2)	27.6 (9.2)	26.3 (8.6)	29.2 (9.1)	27.9 (9.5)	26.4 (8.2)
Previous hospitalizations, n (%)						
0	10 (7.9)	23 (11.6)	8 (14.3)	14 (13.1)	22 (10.8)	4 (7.1)
1	20 (15.9)	45 (22.6)	9 (16.1)	24 (22.4)	49 (24.1)	11 (19.6)
2	21 (16.7)	30 (15.1)	9 (16.1)	19 (17.8)	34 (16.7)	8 (14.3)
3	27 (21.4)	23 (11.6)	6 (10.7)	17 (15.9)	26 (12.8)	10 (17.9)
≥4	48 (38.1)	78 (39.2)	24 (42.9)	33 (30.8)	72 (35.5)	23 (41.1)

Notes: [a]The "Prior other AP" group includes patients who received the following medications within 2 weeks before start of double-blind study medication: amisulpride, aripiprazole, chlorpromazine, chlorprothixene, clotiapine, flupentixol, fluphenazine, haloperidol, haloperidol decanoate, levomepromazine, loxapine, melperone, olanzapine, perazine, perphenazine, promazine, promethazine, quetiapine, risperidone (included because it was not the only antipsychotic used in this population), sertindole, sulpiride, and thioridazine.

Abbreviations: AP, antipsychotic; Ris, risperidone; RLAI, risperidone long-acting injectable; SD, standard deviation.

Thirteen-week completion rates ranged from 79% to 88% across the subgroups analyzed (Table 2). The most common reason for discontinuation in subjects who had received oral risperidone only during the 2 weeks before starting double-blind study medication was withdrawal of consent (6.3% in the paliperidone palmitate group; 5.6% in the RLAI group), whereas in subjects who had received other antipsychotics, the reason was lack of efficacy (7.5% in the paliperidone palmitate group; 6.4% in the RLAI group). Discontinuation rates due to adverse events were low across all subgroups analyzed (range 0%–3.6%, Table 2). One subject from the original study who died met the inclusion criteria for this

Table 2 Patient disposition and study medication exposure

	Paliperidone palmitate			RLAI		
	Prior Ris only (n = 126)	Prior other AP[a] (n = 199)	No prior AP (n = 56)	Prior Ris only (n = 107)	Prior other AP[a] (n = 203)	No prior AP (n = 56)
Disposition						
Completed, n (%)	111 (88.1)	166 (83.4)	44 (78.6)	93 (86.9)	171 (84.2)	46 (82.1)
Discontinued, n (%)	15 (11.9)	33 (16.6)	12 (21.4)	14 (13.1)	32 (15.8)	10 (17.9)
Lack of efficacy	1 (0.8)	15 (7.5)	1 (1.8)	4 (3.7)	13 (6.4)	1 (1.8)
Withdrew consent	8 (6.3)	10 (5.0)	2 (3.6)	6 (5.6)	12 (5.9)	3 (5.4)
AE	1 (0.8)	5 (2.5)	0	0	2 (1.0)	2 (3.6)
Lost to follow-up	1 (0.8)	2 (1.0)	4 (7.1)	1 (0.9)	2 (1.0)	2 (3.6)
Death	0	0	1 (1.8)	0	0	0
Other	4 (3.2)	1 (0.5)	4 (7.1)	3 (2.8)	3 (1.5)	2 (3.6)
Study medication exposure						
Mean dose, mean (SD), mg	115.8 (7.2)	115.2 (7.7)	114.8 (6.5)	28.5 (4.9)	28.2 (4.6)	27.4 (4.2)
Final dose, mean (SD), mg	112.3 (24.2)	109.8 (23.9)	106.3 (21.5)	31.9 (9.6)	31.5 (9.2)	29.7 (8.1)
Total exposure, mean (SD), days	88.3 (12.0)	87.1 (14.2)	86.2 (15.3)	88.1 (13.4)	86.6 (14.7)	84.9 (17.2)

Notes: [a]The "Prior other AP" group includes patients who received the following medications within 2 weeks before start of double-blind study medication: amisulpride, aripiprazole, chlorpromazine, chlorprothixene, clotiapine, flupentixol, fluphenazine, haloperidol, haloperidol decanoate, levomepromazine, loxapine, melperone, olanzapine, perazine, perphenazine, promazine, promethazine, quetiapine, risperidone (included because it was not the only antipsychotic used in this population), sertindole, sulpiride, and thioridazine.

Abbreviations: AE, adverse event; AP, antipsychotic; Ris, risperidone; RLAI, risperidone long-acting injectable; SD, standard deviation.

analysis. Details have been reported elsewhere.[21] Exposure to the study medication (paliperidone palmitate or RLAI) is outlined in Table 2. For subjects in the prior risperidone only population, the mean modal dose of risperidone within 2 weeks before the start of double-blind study medication was 5.2 ± 3.2 mg for the paliperidone palmitate group and 5.0 ± 3.1 mg for the RLAI group.

Efficacy

Baseline scores for each of the efficacy measures for both the RLAI and paliperidone palmitate treatment groups are outlined in Table 3. Improvement in PANSS total, PANSS factors, and CGI-S scale scores from baseline to end point was significant for both paliperidone palmitate and RLAI treatment groups (all $P \leq 0.0002$), regardless of whether subjects had received recent prior treatment with oral risperidone only, other antipsychotics, or no antipsychotic in the 2 weeks before starting double-blind study medication (Table 3). Responder rates at end point ranged from 48.2% to 66.1% across groups (Table 3). The distribution of categorical CGI-S scores (Figure 1) showed improvements that were similar by inspection from baseline to end point for both the paliperidone palmitate and RLAI subpopulations, regardless of whether subjects had previously received risperidone only, other antipsychotics, or no antipsychotics.

Functioning

PSP scale scores significantly improved from baseline to end point among all previous treatment subgroups for both paliperidone palmitate and RLAI treatment groups (all $P < 0.0001$, Table 3). The distribution of categorical PSP scale scores (Figure 2) showed improvement across all groups.

Safety

From 52% to 61% of subjects across the six subgroups analyzed experienced at least one treatment-emergent adverse event. The most common adverse events, and those of particular interest (extrapyramidal symptoms, prolactin-related and glucose-related adverse events), are outlined in Table 4. Common adverse events for paliperidone palmitate subjects were insomnia, headache, and injection site pain, irrespective of prior oral risperidone status. Common adverse events for all RLAI subjects were insomnia and headache.

Discussion

This post hoc subgroup analysis of a 13-week trial demonstrates that treatment with monthly paliperidone palmitate or biweekly RLAI effectively reduced symptoms of schizophrenia independently of whether previous treatment consisted of oral risperidone only or oral antipsychotics, or whether no immediate previous treatment had been received. The robustness of this result is supported by findings of consistent symptom improvement across all efficacy measures used (PANSS and CGI-S) and by the functioning outcome measured by the PSP scale. Of particular interest is the finding that symptom reduction was similar for the groups receiving an oral form of an identical or chemically related molecule both before and after randomization to long-acting injection (risperidone followed by RLAI, and risperidone followed by paliperidone palmitate). This supports the clinical value of initiating long-acting injectable treatment in subjects who have not achieved adequate symptom control with an identical or chemically related oral antipsychotic, despite the similarities in mechanisms of action. Of note, our analysis is consistent with other studies of injectable formulations of paliperidone palmitate and risperidone that report successful symptom reduction in subjects who had remained symptomatic after therapy with a related oral molecule.[27–31] However, it is relevant to note here that published findings from direct comparisons of long-acting injectable and oral antipsychotics have yielded conflicting results.[9,32,33]

This analysis included data on patients who were not taking oral antipsychotics immediately before entering the trial. This clinically relevant patient population might be expected to respond well after starting paliperidone palmitate or RLAI, or even better than those patients who were symptomatic despite treatment with oral antipsychotics. The similarity in response to paliperidone palmitate and RLAI seen in these patients compared with those who had been receiving risperidone only or other antipsychotics suggests that the lack of efficacy that the majority of patients experienced using oral antipsychotics before study entry, particularly risperidone, was due to some reason other than lack of pharmacologic action.

Poor adherence to prescribed treatment is a well-recognized problem for subjects with schizophrenia. At least one-third of subjects struggle to adhere adequately to treatment after only a few weeks of therapy, and only one-quarter remain fully adherent 2 years after initiating therapy.[3,7] Nonadherence to medication can result in increased hospitalizations (both psychiatric and nonpsychiatric),[5] exacerbation of schizophrenia symptoms, and poor functional outcomes.[7] Subjects who remained symptomatic after oral risperidone may have benefited from treatment with extended-release oral formulations of paliperidone palmitate because of

Table 3 Efficacy outcomes

	Paliperidone palmitate			RLAI		
	Prior Ris only (n = 126)	Prior other AP[a] (n = 199)	No prior AP (n = 56)	Prior Ris only (n = 107)	Prior other AP[a] (n = 203)	No prior AP (n = 56)
PANSS total, mean (SD)						
Baseline	84.3 (11.2)	85.3 (11.7)	84.9 (12.1)	83.7 (10.4)	83.2 (10.9)	83.9 (11.3)
Change from baseline to end point	−18.7 (13.7)[b]	−18.5 (17.3)[b]	−19.5 (12.8)[b]	−18.3 (13.2)[b]	−17.6 (14.1)[b]	−17.5 (16.1)[b]
PANSS positive symptoms, mean (SD)						
Baseline	23.3 (4.5)	24.3 (4.8)	24.4 (4.3)	23.8 (4.6)	23.6 (4.5)	24.1 (4.4)
Change from baseline to end point	−5.6 (4.8)[b]	−6.2 (5.8)[b]	−6.2 (4.5)[b]	−5.8 (4.7)[b]	−5.7 (4.8)[b]	−5.9 (4.9)[b]
PANSS negative symptoms, mean (SD)						
Baseline	22.7 (4.6)	22.2 (4.6)	21.4 (5.2)	22.0 (4.7)	21.8 (4.4)	21.2 (4.6)
Change from baseline to end point	−4.6 (3.8)[b]	−4.0 (5.2)[b]	−3.9 (3.8)[b]	−4.0 (4.3)[b]	−4.2 (4.2)[b]	−3.6 (4.8)[b]
PANSS disorganized thought, mean (SD)						
Baseline	19.9 (3.8)	20.3 (3.7)	19.6 (3.9)	19.8 (3.7)	19.7 (3.7)	19.4 (3.5)
Change from baseline to end point	−3.7 (3.6)[b]	−3.5 (4.4)[b]	−4.1 (3.6)[b]	−4.0 (3.5)[b]	−3.4 (3.5)[b]	−3.0 (4.5)[b]
PANSS uncontrolled hostility/excitement, mean (SD)						
Baseline	8.5 (2.9)	8.5 (3.0)	8.8 (2.8)	8.4 (2.7)	8.2 (3.0)	8.9 (2.8)
Change from baseline to end point	−1.9 (2.8)[b]	−1.9 (3.0)[b]	−1.9 (2.4)[b]	−2.1 (2.4)[b]	−1.6 (3.0)[b]	−1.7 (3.1)[b]
PANSS anxiety/depression, mean (SD)						
Baseline	9.9 (2.5)	10.1 (2.7)	10.6 (2.2)	9.7 (2.7)	9.8 (2.5)	10.3 (2.4)
Change from baseline to end point	−3.0 (2.5)[b]	−2.8 (3.3)[b]	−3.4 (2.8)[b]	−2.4 (2.5)[b]	−2.6 (2.8)[b]	−3.4 (2.6)[b]
CGI-S, mean (SD)						
Baseline	4.2 (0.6)	4.3 (0.6)	4.3 (0.8)	4.2 (0.7)	4.2 (0.7)	4.2 (0.6)
Change from baseline to end point	−1.0 (0.9)[b]	−1.0 (1.0)[b]	−1.1 (0.9)[b]	−1.0 (0.9)[b]	−0.9 (0.9)[b]	−0.9 (0.9)[b]
PSP, mean (SD)						
Baseline	55.5 (12.6)	52.8 (11.7)	56.6 (12.5)	55.7 (11.1)	54.5 (12.6)	56.9 (12.0)
Change from baseline to end point	9.9 (10.5)[b]	9.7 (11.8)[b]	8.6 (10.7)[b]	9.9 (10.7)[b]	9.2 (11.2)[b]	10.5 (10.5)[b]
Responder rate at end point[c], n (%)	72 (57.1)	107 (53.8)	37 (66.1)	56 (52.3)	108 (53.2)	27 (48.2)

Notes: [a]The "Prior other AP" group includes patients who received the following medications within 2 weeks before start of double-blind study medication: amisulpride, aripiprazole, chlorpromazine, chlorprothixene, clotiapine, flupentixol, fluphenazine, haloperidol, haloperidol decanoate, levomepromazine, loxapine, melperone, olanzapine, perazine, perphenazine, promazine, promethazine, quetiapine, risperidone (included because it was not the only antipsychotic used in this population), sertindole, sulpiride, and thioridazine; [b]$P \leq 0.0002$, baseline to end point; [c]proportion of subjects with ≥30% improvement at end point in PANSS total score.

Abbreviations: AP, antipsychotic; CGI-S, Clinical Global Impressions–Severity scale; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance scale; Ris, risperidone; RLAI, risperidone long-acting injectable; SD, standard deviation.

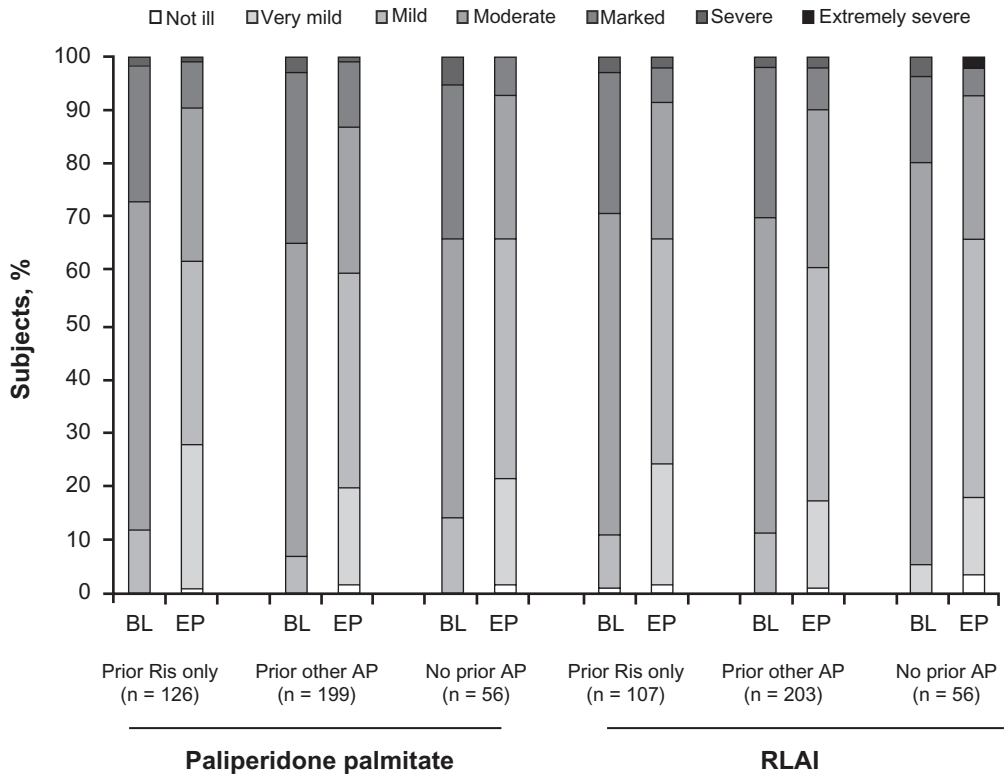

Figure 1 Categorical CGI-S scores from baseline to end point.
Abbreviations: AP, antipsychotic; BL, baseline; CGI-S, Clinical Global Impression–Severity scale; EP, end point; Ris, risperidone; RLAI, risperidone long-acting injectable.

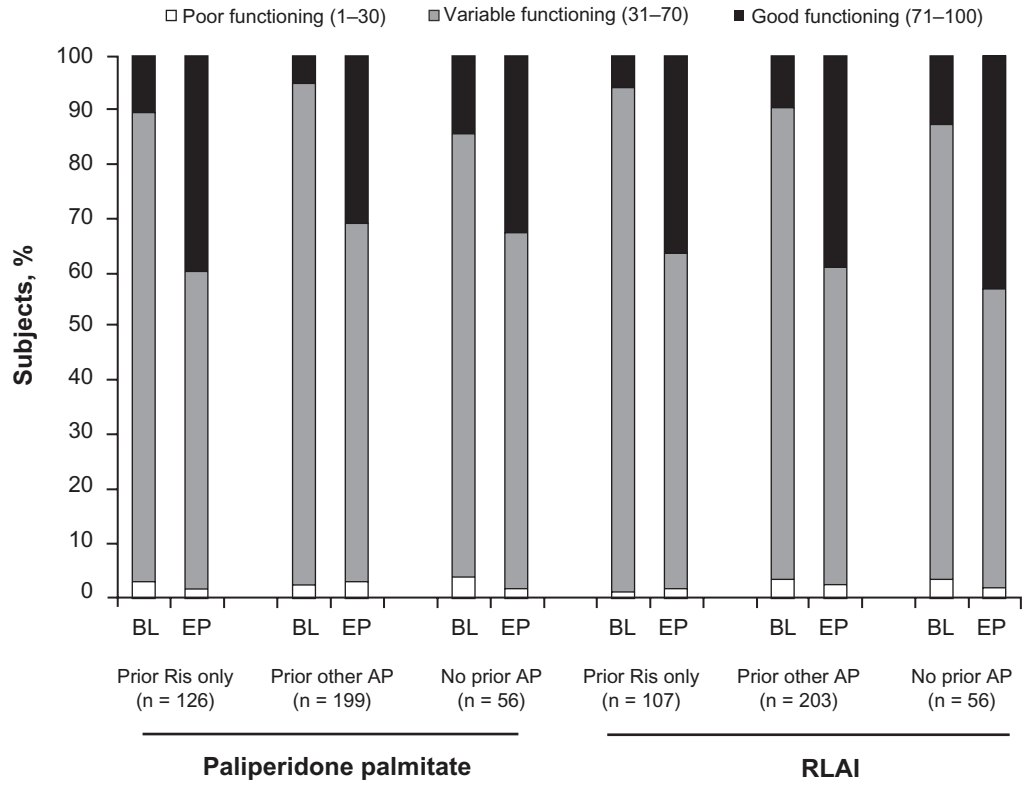

Figure 2 Categorical PSP scale score from baseline to end point.
Abbreviations: AP, antipsychotic; BL, baseline; PSP, Personal and Social Performance; EP, end point; Ris, risperidone; RLAI, risperidone long-acting injectable.

Table 4 Treatment-emergent adverse events

	Paliperidone palmitate			RLAI		
n (%)	Prior Ris only (n = 126)	Prior other AP[a] (n = 199)	No prior AP (n = 56)	Prior Ris only (n = 107)	Prior other AP[a] (n = 203)	No prior AP (n = 56)
Subjects with ≥1 AE	68 (54.0)	122 (61.3)	31 (55.4)	56 (52.3)	109 (53.7)	29 (51.8)
Discontinuation due to AEs	1 (0.8)	5 (2.5)	0	0	2 (1.0)	2 (3.6)
Most common AEs (≥5% in any group)						
Headache	8 (6.3)	18 (9.0)	5 (8.9)	6 (5.6)	19 (9.4)	3 (5.4)
Insomnia	13 (10.3)	25 (12.6)	4 (7.1)	6 (5.6)	17 (8.4)	4 (7.1)
Injection site pain	9 (7.1)	6 (3.0)	6 (10.7)	0	2 (1.0)	0
Somnolence	5 (4.0)	12 (6.0)	3 (5.4)	6 (5.6)	7 (3.4)	1 (1.8)
Akathisia	5 (4.0)	13 (6.5)	3 (5.4)	4 (3.7)	7 (3.4)	1 (1.8)
Schizophrenia	3 (2.4)	11 (5.5)	1 (1.8)	3 (2.8)	7 (3.4)	2 (3.6)
Salivary hypersecretion	1 (0.8)	7 (3.5)	3 (5.4)	3 (2.8)	0	1 (1.8)
Weight increased	5 (4.0)	3 (1.5)	3 (5.4)	2 (1.9)	3 (1.5)	3 (5.4)
Nasopharyngitis	2 (1.6)	5 (2.5)	2 (3.6)	2 (1.9)	4 (2.0)	3 (5.4)
Lethargy	2 (1.6)	2 (1.0)	0	0	0	4 (7.1)
Tremor	0	8 (4)	3 (5.4)	2 (1.9)	5 (2.5)	0
Subjects with ≥1 EPS-related AE	10 (7.9)	31 (15.6)	9 (16.1)	9 (8.4)	22 (10.8)	2 (3.6)
Most common EPS-related AEs (≥2% in any group)						
Akathisia	5 (4.0)	13 (6.5)	3 (5.4)	4 (3.7)	7 (3.4)	1 (1.8)
Muscle rigidity	2 (1.6)	3 (1.5)	1 (1.8)	3 (2.8)	3 (1.5)	0
Muscle tightness	0	1 (0.5)	2 (3.6)	0	1 (0.5)	0
Musculoskeletal stiffness	2 (1.6)	1 (0.5)	2 (3.6)	1 (0.9)	0	0
Tremor	0	8 (4.0)	3 (5.4)	2 (1.9)	5 (2.5)	0
Parkinsonism	0	5 (2.5)	1 (1.8)	0	2 (1.0)	0
Subjects with ≥1 prolactin-related AE	2 (1.6)	6 (3.0)	2 (3.6)	2 (1.9)	5 (2.5)	4 (7.1)
Most common prolactin-related AEs (≥1% in any group)						
Amenorrhea	0	2 (1.0)	1 (1.8)	1 (0.9)	2 (1.0)	1 (1.8)
Anorgasmia	0	1 (0.5)	0	0	0	1 (1.8)
Erectile dysfunction	1 (0.8)	0	0	1 (0.9)	1 (0.5)	1 (1.8)
Galactorrhea	0	0	0	0	0	1 (1.8)
Ejaculation delayed	0	0	1 (1.8)	0	0	0
Libido decreased	1 (0.8)	2 (1.0)	0	0	1 (0.5)	0
Subjects with ≥1 glucose-related AE	0	1 (0.5)[b]	0	0	0	0

Notes: [a]The "Prior other AP" group includes patients who received the following medications within 2 weeks before start of double-blind study medication: amisulpride, aripiprazole, chlorpromazine, chlorprothixene, clotiapine, flupentixol, fluphenazine, haloperidol, haloperidol decanoate, levomepromazine, loxapine, melperone, olanzapine, perazine, perphenazine, promazine, promethazine, quetiapine, risperidone (included because it was not the only antipsychotic used in this population), sertindole, sulpiride, and thioridazine; [b]one subject had an increased blood glucose level.

Abbreviations: AE, adverse event; AP, antipsychotic; EPS, extrapyramidal symptom; Ris, risperidone; RLAI, risperidone long-acting injectable.

improved pharmacokinetics and tolerability.[34,35] However, this formulation still requires daily dosing. Long-acting injectable medications can further help overcome problems with nonadherence by removing the need for daily dosing and by simplifying treatment.[3,7] Because the health care provider can know with certainty whether a patient has received an injection, use of long-acting injectable antipsychotics provides clinicians with definitive information on patient adherence to medication. This removes the need for ongoing discussion of the need for medication and careful adherence to its use,[3,36] and patient contact with treatment teams can be more focused on providing psychoeducation and social skills training.[3] Further, there is a potential health economic advantage of knowing that a prescribed medication has been taken rather than discarded or left unused in a medicine cabinet.

Another possible reason for improved treatment response to paliperidone palmitate or RLAI in subjects with a recent history of suboptimal response to treatment with oral risperidone is that long-acting injectable formulations provide more continuous delivery of medication without daily peaks and troughs.[37,38] Depot injections improve the bioavailability of antipsychotics, which typically have variable bioavailability when taken orally because of nonspecific metabolism in the gut wall and first-pass hepatic metabolism.[37,39] Increased

bioavailability means that lower total drug doses may be required to achieve similar clinical outcomes because a greater portion of the dose is available to the central nervous system.[39] The reduction in daily peak and trough blood levels compared with oral compounds may contribute to fewer adverse events and again to better long-term compliance.[37] Interestingly, discontinuations due to lack of efficacy were no more frequent in the prior oral risperidone only subgroups than in those receiving alternative prior treatments. Lack of efficacy might have been expected to be greater in these subjects because only the method of delivery of similar molecules was changed. This finding highlights the importance of formulation considerations when treating subjects with schizophrenia.

Tolerability and safety in this subgroup analysis were consistent with findings from the overall study population.[21] Injection site pain was reported more frequently by subjects in the paliperidone palmitate subgroups than by those receiving RLAI (range 3.0–10.7% vs 0–1.0%, respectively). This may have been due to the initial injection site for the active treatment (deltoid for paliperidone palmitate vs gluteal for RLAI), because gluteal injections have been reported to be somewhat better tolerated than deltoid injections.[40]

Limitations

The original study was not designed to examine subjects by prior oral antipsychotic treatment and, therefore, complete information on prior treatment (including dose, duration, and adherence) was not systematically collected. Available information was dependent on retrospective subject or clinician reports. For this reason, it was not possible to determine whether the duration and dose of prior treatment with risperidone only or other antipsychotics had been optimized before switching to the long-acting study medication. In addition, it is possible that the observed improvements with paliperidone palmitate and RLAI were due in part to study participation and regression to the mean. However, given that improvements were seen across all treatment groups and were consistent across multiple measures (psychotic symptoms, global status, and functioning), this seems unlikely. A comparator group with oral antipsychotic treatment could have helped clarify these limitations to interpretation. Finally, although numerical differences were noted in the distribution of gender and race between the subgroups, significant improvements in schizophrenia symptoms were seen in every subgroup analyzed, making further exploration of these baseline characteristics unnecessary.

In conclusion, this post hoc analysis of a 13-week trial suggests that treatment with paliperidone palmitate or RLAI can be effective in subjects regardless of which oral antipsychotic treatment they have received. For patients who had previously received oral risperidone only, the difference in formulation was the main change in the intervention, because the molecule delivered remained the same or similar. These data support the contribution of a long-acting formulation to improved treatment response, and suggest that nonadherence may be a significant contributor to inadequate efficacy of oral formulations in subjects with schizophrenia.

Acknowledgment

The authors wish to acknowledge Matthew Grzywacz and Alison Comer of ApotheCom (funded by Janssen Scientific Affairs LLC) for providing writing and editorial assistance.

Disclosure

This study was supported by Janssen Scientific Affairs LLC. LA, D-JF, CAB, JKS, and JH are employees of Janssen Scientific Affairs LLC, and are Johnson & Johnson stockholders. Y-WM is an employee of Janssen Research & Development LLC, and is a Johnson & Johnson stockholder.

References

1. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209–1223.
2. Lindenmayer JP, Liu-Seifert H, Kulkarni PM, et al. Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. *J Clin Psychiatry*. 2009;70:990–996.
3. Nasrallah HA. The case for long-acting antipsychotic agents in the post-CATIE era. *Acta Psychiatr Scand*. 2007;115:260–267.
4. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. *Psychiatry Res*. 2010;176:109–113.
5. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv*. 2004;55:886–891.
6. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36:71–93.
7. Velligan DI, Weiden PJ, Sajatovic M, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry*. 2009;70:1–46.
8. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia – a critical systematic review and meta-analysis of randomised long-term trials. *Schizophr Res*. 2011;127:83–92.
9. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry*. 2011;168:603–609.
10. Kane JM, Eerdekens M, Lindenmayer JP, Keith SJ, Lesem M, Karcher K. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry*. 2003;160:1125–1132.

11. Simpson GM, Mahmoud RA, Lasser RA, et al. A 1-year double-blind study of 2 doses of long-acting risperidone in stable patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry*. 2006;67:1194–1203.
12. Fleischhacker WW, Eerdekens M, Karcher K, et al. Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. *J Clin Psychiatry*. 2003;64:1250–1257.
13. Kramer M, Litman R, Hough D, et al. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. *Int J Neuropsychopharmacol*. 2010;13:635–647.
14. Gopal S, Hough DW, Xu H, et al. Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study. *Int Clin Psychopharmacol*. 2010;25:247–256.
15. Pandina GJ, Lindenmayer JP, Lull J, et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. *J Clin Psychopharmacol*. 2010;30:235–244.
16. Citrome L. Paliperidone palmitate – review of the efficacy, safety and cost of a new second-generation depot antipsychotic medication. *Int J Clin Pract*. 2010;64:216–239.
17. Gopal S, Gassmann-Mayer C, Palumbo J, Samtani MN, Shiwach R, Alphs L. Practical guidance for dosing and switching paliperidone palmitate treatment in patients with schizophrenia. *Curr Med Res Opin*. 2010;26:377–387.
18. Hough D, Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *Schizophr Res*. 2010;116:107–117.
19. Janssen Pharmaceuticals Inc. Invega® Sustenna® (paliperidone palmitate) extended-release injectable suspension. Titusville, NJ: Janssen Pharmaceuticals Inc; Aug 2012.
20. Janssen Pharmaceuticals Inc. Risperdal® Consta® (risperidone) long-acting injection. Titusville, NJ: Janssen Pharmaceuticals Inc; Jun 2012.
21. Pandina G, Lane R, Gopal S, et al. A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35:218–226.
22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association; 2000.
23. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261–276.
24. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry*. 1997;58:538–546.
25. Guy W. *ECDEU Assessment Manual for Psychopharmacology (028 Clinical Global Impressions [CGI])*. 1976:218–222.
26. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV social and occupational functioning assessment scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand*. 2000;101:323–329.
27. Sliwa JK, Bossie CA, Ma YW, Alphs L. Effects of acute paliperidone palmitate treatment in subjects with schizophrenia recently treated with oral risperidone. *Schizophr Res*. 2011;132:28–34.
28. Moller HJ, Llorca PM, Sacchetti E, Martin SD, Medori R, Parellada E. Efficacy and safety of direct transition to risperidone long-acting injectable in patients treated with various antipsychotic therapies. *Int Clin Psychopharmacol*. 2005;20:121–130.
29. van Os J, Bossie CA, Lasser RA. Improvements in stable patients with psychotic disorders switched from oral conventional antipsychotics therapy to long-acting risperidone. *Int Clin Psychopharmacol*. 2004;19:229–232.
30. De Marinis T, Saleem PT, Glue P, et al. Switching to long-acting injectable risperidone is beneficial with regard to clinical outcomes, regardless of previous conventional medication in patients with schizophrenia. *Pharmacopsychiatry*. 2007;40:257–263.
31. Schmauss M, Sacchetti E, Kahn JP, Medori R. Efficacy and safety of risperidone long-acting injectable in stable psychotic patients previously treated with oral risperidone. *Int Clin Psychopharmacol*. 2007;22:85–92.
32. Grimaldi-Bensouda L, Rouillon F, Astruc B, et al. Does long-acting injectable risperidone make a difference to the real-life treatment of schizophrenia? Results of the Cohort for the General study of Schizophrenia (CGS). *Schizophr Res*. 2012;134:187–194.
33. Rosenheck RA, Krystal JH, Lew R, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med*. 2011;364:842–851.
34. Canuso CM, Grinspan A, Kalali A, et al. Medication satisfaction in schizophrenia: a blinded-initiation study of paliperidone extended release in patients suboptimally responsive to risperidone. *Int Clin Psychopharmacol*. 2010;25:155–164.
35. Canuso CM, Youssef EA, Bossie CA, Turkoz I, Schreiner A, Simpson GM. Paliperidone extended-release tablets in schizophrenia patients previously treated with risperidone. *Int Clin Psychopharmacol*. 2008;23:209–215.
36. Kane JM, Garcia-Ribera C. Clinical guideline recommendations for antipsychotic long-acting injections. *Br J Psychiatry Suppl*. 2009;52:S63–S67.
37. Ereshefsky L, Mascarenas CA. Comparison of the effects of different routes of antipsychotic administration on pharmacokinetics and pharmacodynamics. *J Clin Psychiatry*. 2003;64:18–23.
38. Samtani MN, Vermeulen A, Stuyckens K. Population pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia: a novel once-monthly, long-acting formulation of an atypical antipsychotic. *Clin Pharmacokinet*. 2009;48:585–600.
39. McEvoy JP. Risks versus benefits of different types of long-acting injectable antipsychotics. *J Clin Psychiatry*. 2006;67 Suppl 5:15–18.
40. Hough D, Lindenmayer JP, Gopal S, et al. Safety and tolerability of deltoid and gluteal injections of paliperidone palmitate in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33:1022–1031.