Paliperidone Palmitate versus Risperidone Long-Acting Injection in Markedly-to-Severely Ill Schizophrenia Subjects: Onset of Efficacy with Recommended Initiation Regimens

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Abstract

Objective: To examine onset of efficacy of two long-acting injectable atypical antipsychotics in markedly-to-severely ill schizophrenia subjects. **Methods:** This subgroup analysis included 292 subjects with baseline Clinical Global Impressions-Severity scores of markedly ill or worse from a 13-week, randomized, double-dummy noninferiority study (NCT00589914). Subjects received either: 1) paliperidone palmitate (PP; 234 mg day 1 and 156 mg day 8 [corresponding to 150 and 100 milligram equivalents of paliperidone, respectively], both administered in deltoid muscle, followed by once-monthly flexible dosing in deltoid or gluteal muscle) and risperidone long-acting injection (RLAI)–matched placebo injections; or, 2) RLAI (25 mg, days 8 and 22; followed by biweekly flexible dosing) and PP-matched placebo injections. RLAI subjects received oral risperidone days 1–28; PP subjects received oral placebo. Because of RLAI's release profile, data through day 22 correspond to oral risperidone. Assessments included Positive and Negative Syndrome Scale (PANSS) and adverse event (AE) reports. Paired t-tests assessed within-group changes. **Results:** LS mean (SE) PANSS total scores improved significantly (both p<.001) with PP and oral risperidone by day 4 (-5.0 [0.6] and -3.4 [0.6], respectively) through day 22; and with PP and RLAI through end point (-21.5 [1.9] and -18.6 [1.9], respectively). The between-group difference was significant only at day 4 (p=.006). Proportion of subjects with a ≥30% reduction in PANSS total score was not significantly different between the two groups at day 4 and was significantly greater with paliperidone palmitate than oral risperidone at days 15 and 22 (26.1% versus 12.7%, p=.013; 41.6% versus 32.0%, p=.048, respectively). Most common AEs (≥5% in either treatment group): headache (PP 6.3% and RLAI 14.0%), insomnia (10.6% and 10.7%), somnolence (7.8% and 1.3%), akathisia (7.0% and 5.3%), schizophrenia (8.5% and 5.3%), agitation (5.6% and 2.0%), and injection site pain (5.6% and 1.3%). **Conclusions:** Using the recommended dosing regimens for PP and RLAI, both PP and oral risperidone (used during RLAI initiation) improved symptoms of schizophrenia in markedly-to-severely ill subjects at days 4–22.

Introduction

Long-acting injectable antipsychotics, although established agents for the treatment of schizophrenia, differ in their formulation, release profile, pharmacodynamics, and dosing

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regimens—and thus in their ability to provide rapid symptom control. To address the latter, the initiation regimens of these agents are often designed to ensure that therapeutic drug levels are achieved rapidly, so that most patients experience the drug's efficacy within the first few days of treatment (1, 2). Rapid symptom control in patients with schizophrenia is often an immediate treatment goal, especially for those who are particularly ill. The impact of inadequate treatment may be serious, contributing to relapse, hospitalization, incarceration, loss of function, and suicidality (3, 4).

Although numerous factors may lead to inadequate symptom control, nonadherence with medication is often a

Clinical Implications

This subgroup analysis of markedly-to-severely ill subjects with schizophrenia suggests that paliperidone palmitate administered once monthly after initiation injections (234 mg on day 1, followed by 156 mg 1 week later) improved symptoms as effectively as risperidone long-acting injection (RLAI) administered biweekly with oral risperidone supplementation for the first 3 weeks. The onset of efficacy as measured by significant improvements in efficacy scales was observed by day 4 in both groups, with significant improvements also noted through day 22. Of note, this finding was consistent with the PANSS rating of symptoms as well as the CGI-S rating of overall clinical status. Because of the release profile of RLAI, these first few weeks actually provide a comparison of the effect of paliperidone palmitate to that of oral risperidone up to the day 22 time point. There was no indication that paliperidone palmitate without oral supplementation might have a slower onset of efficacy than oral risperidone. In fact, the change in PANSS total score was greater at day 4 for the paliperidone palmitate group, with no significant between-group differences at subsequent time points in this 13-week study.

The clinical advantages of the combined attributes of early onset of action with persistence of effect after the initiation regimen observed following paliperidone palmitate treatment without supplementation require further exploration. Results will provide additional guidance to clinicians who are considering the management of symptomatic patients with paliperidone palmitate relative to alternative approaches.

key contributor for many patients with schizophrenia. Many variables can play a role in nonadherence, such as forgetfulness, lack of social support, lack of insight regarding one's illness or the need for medication, tolerability issues, and refractory or nonresponsive symptomatology (5-8). Long-acting injectable antipsychotics can address some barriers to adherence by obviating the need for daily medication. In addition, there is no gut absorption or first-pass hepatic metabolism with long-acting injectable agents, which contributes to a more predictable bioavailability. This can result in similar outcomes at lower dose exposures than with oral agents (9, 10).

Paliperidone palmitate and risperidone long-acting injection (RLAI) are two long-acting injectable atypical antipsychotics that are effective in treating schizophrenia (11-16). These agents, while related molecules, have different pharmacologic, pharmacokinetic (PK), and formulation delivery profiles, with distinct initiation and maintenance regimens (17-20). Placebo-controlled studies show that paliperidone palmitate is effective for the treatment of patients with acutely symptomatic schizophrenia and also as maintenance therapy (14-16, 21). Paliperidone palmitate is an ester of paliperidone formulated as a NanoCrystal® suspension (22) (Janssen, data on file) in an aqueous environment whereby active drug is released after being hydrolyzed by endogenous esterases (23). To ensure rapid attainment of therapeutic plasma levels, the recommended initiation regimen requires initial doses of 234 mg on day 1 and 156 mg on day 8 (both deltoid), followed by once-monthly doses of 39 mg to 234 mg (deltoid or gluteal) (23). In contrast, RLAI is encapsulated in biodegradable microspheres suspended in an aqueous solution and the release of risperidone occurs by hydrolysis of the microspheres. Since less than 1% of the risperidone is released from the RLAI mi-

crospheres in the first 3 weeks of RLAI treatment (24), this agent requires supplementation with an oral antipsychotic for the first 3 weeks to ensure therapeutic levels of active drug for early symptom control. RLAI is administered biweekly, with a recommended starting dose of 25 mg in the deltoid or gluteal muscle and higher doses of 37.5 mg or 50 mg, as required (24). Placebo-controlled studies have shown that RLAI is efficacious and tolerable for patients with schizophrenia and for maintenance treatment of patients with bipolar I disorder as monotherapy or as adjunctive therapy with lithium or valproate (11, 12, 25, 26).

The objective of the current post hoc analysis is to evaluate the onset of efficacy and tolerability for both injectable paliperidone palmitate and RLAI in markedly-to-severely ill subjects with schizophrenia. This subgroup from a larger double-blind study population was selected for analysis because it represents a subgroup for whom rapid symptom control is particularly important. The original study showed that paliperidone palmitate was not inferior to RLAI in subjects with acute schizophrenia (27). We hypothesized that during the initial treatment period, paliperidone palmitate without oral supplementation would be as efficacious as RLAI, which needs oral supplementation.

Methods
Study Design

This was a subgroup analysis of a 13-week, randomized, double-blind, double-dummy, parallel-group, multicenter comparative study. Results of the original study population have been previously presented (NCT00589914) (27). Adults who met the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* criteria for schizophrenia for at least 1 year and had a Positive and Negative Syndrome Scale

(PANSS) total score of 60 to 120 inclusive at screening were enrolled. Subjects were randomized in a 1:1 ratio to paliperidone palmitate or RLAI treatment (see Figure 1). This subgroup analysis focused on subjects with a Clinical Global Impressions-Severity (CGI-S) score ≥5 (markedly-to-severely ill) at baseline.

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable regulatory requirements. All subjects provided written informed consent before entering the study.

Study Medication

Paliperidone palmitate was initiated by doses of 234 mg on day 1 and 156 mg on day 8 injected into the deltoid muscle, followed by once-monthly flexible doses injected into the deltoid or gluteal muscle on day 36 (78 mg, 156 mg) and day 64 (78 mg, 156 mg, 234 mg) (see Figure 1). Subjects in the paliperidone palmitate group received RLAI-matched placebo gluteal injections and oral risperidone-matched placebo.

RLAI was administered by biweekly gluteal injections of 25 mg starting on day 8, with the next injection on day 22;

25 mg or 37.5 mg on days 36 and 50; and 25 mg, 37.5 mg, or 50 mg on days 64 and 78. The first injection of RLAI was on day 8 (versus day 1) so both treatment groups would subsequently be on the same injection schedules. Because of the release profile of RLAI and the injection schedules in this study, daily oral supplementation with risperidone 1 mg to 6 mg was required on days 1 through 28 in the RLAI group and was optional thereafter with RLAI dose increases. These subjects received paliperidone palmitate-matched placebo injections into the deltoid or gluteal muscle.

Doses of paliperidone palmitate are expressed in milligrams (mg) in this manuscript. Paliperidone palmitate doses may also be expressed in 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 equivalent of paliperidone, respectively.

Except for nonselective or irreversible monoamine oxidase inhibitors, antidepressants were allowed if they had been at stable doses for thirty days or more before screening. Antiparkinsonian treatment of extrapyramidal symptoms and oral benzodiazepines were also allowed. Benzodiazepines were not to be administered within six hours of a scheduled efficacy or safety rating scale.

Figure 1. Study Design and Dosing Schedule
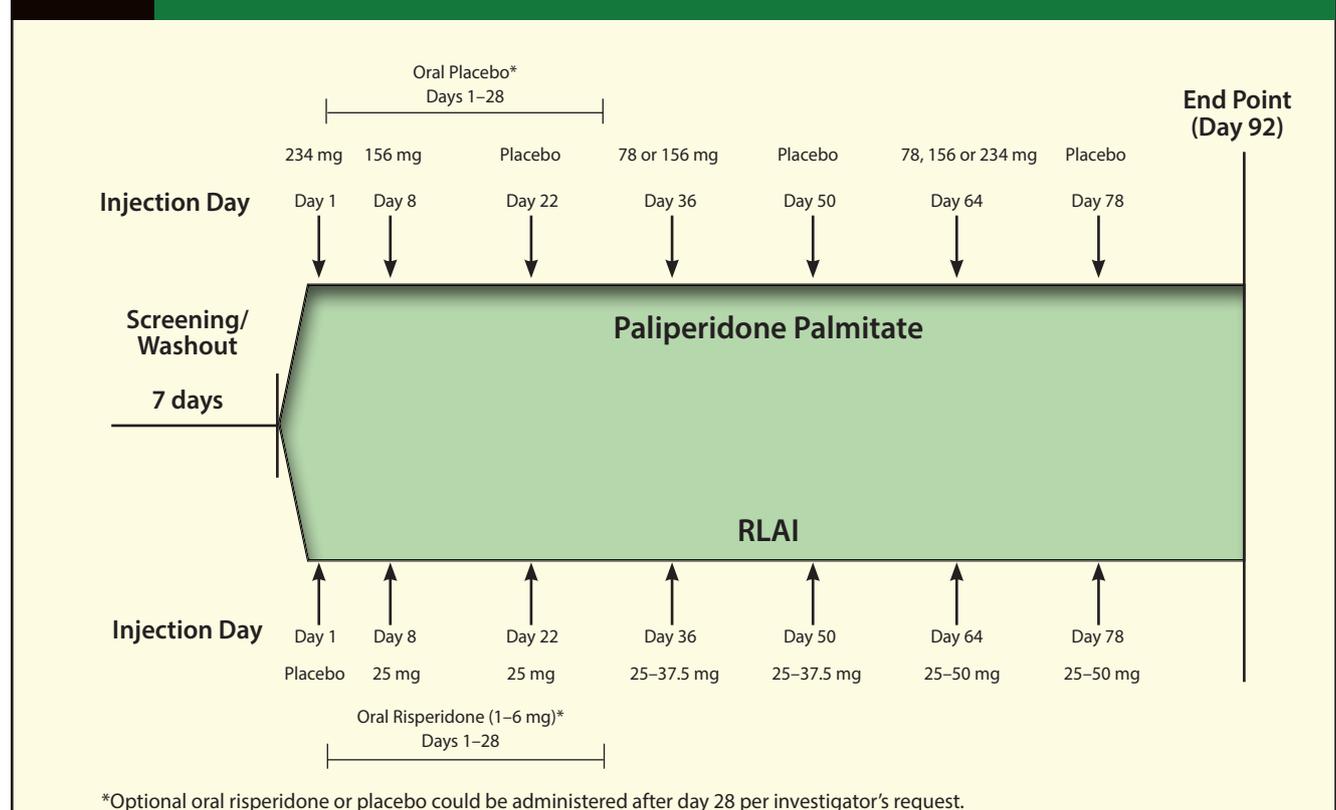
RLAI=risperidone long-acting injection.
Because of the release profile of RLAI (<1% of risperidone is released during the first 3 weeks) (24), paliperidone palmitate could be compared with oral risperidone through day 22. On days 8, 36, and 64, subjects received dual injections to preserve the double-dummy design (27).

Measures

Assessments included the PANSS and CGI-S scores at baseline and days 4, 15, 22, 36, 64, and 92 and the Personal and Social Performance (PSP) scale score at baseline and days 15, 36, 64, and 92. Responders were defined as those subjects with a 30% or greater improvement in PANSS total score from baseline. Movement disorder rating scales included the Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS), and the Abnormal Involuntary Movement Scale (AIMS). Adverse event (AE) reports were collected at each visit.

As detailed in the original study (27), blood samples were taken for PK analysis at baseline, predose before each study drug injection (days 8, 22, 36, 50, 64, 78, and at study end or early withdrawal), and on days 4 and 15. Plasma levels of paliperidone in the paliperidone palmitate group and active moiety (sum of risperidone and paliperidone) in the RLAI group were determined using a validated liquid chromatography coupled to tandem mass spectrometry method with a target limit of quantification of 0.1 ng/mL (28).

Statistical Analysis

Analyses compared the paliperidone palmitate and RLAI groups at baseline and on days 4, 15, 22, 36, 64, and 92 or end point. The analysis set was the intent-to-treat (ITT) population, defined as those subjects who had received at least one dose of double-blind study drug and had both a baseline PANSS measure and at least one post-randomization PANSS measure. This population differed from that used for the primary efficacy analysis set in the original study (27), which included only subjects exposed to the double-blind treatment regimen for a minimum of 36 days. The ITT population was used here in order to include markedly-to-severely ill subjects discontinuing in the first 36 days. Because of the release profile of the study medications and the oral risperidone supplementation in the RLAI group, data through day 22 correspond to oral risperidone in that study group, while data at subsequent time points correspond to the risperidone released from RLAI (and any eventual additional oral risperidone supplementation).

Mean (standard deviation [SD]), median, minimum, and maximum were used for summary of continuous variables; percentage and frequency described categorical variables. Within-group differences were evaluated using a paired t-test. Between-treatment-group differences in continuous variables were evaluated using an analysis of covariance model, with treatment and country as factors and baseline score as a covariate using last observation carried forward (LOCF) methods. Changes from baseline are presented as least-squares (LS) means with standard errors (SEs). Between-treatment-group differences in categorical variables were evaluated using the

Cochran-Mantel-Haenszel test, controlling for country. In the original study analysis (27), noninferiority of paliperidone palmitate was demonstrated if the 95% confidence interval (CI) for the difference in PANSS total score was no more than 5 points worse for paliperidone palmitate compared with RLAI. The same criteria were applied to this subgroup analysis. All statistical tests were two-sided; no adjustments were made for multiplicity.

Results

Of the 913 subjects in the overall study population, 292 (32.0%; paliperidone palmitate, n=142; RLAI, n=150) were rated with marked-to-severe illness at baseline by the CGI-S and were included in this subgroup analysis. Baseline demographics and clinical characteristics were similar between the two treatment groups (see Table 1). Most subjects (88.4%) in this subgroup had marked illness (CGI-S=5), with a mean PANSS score of approximately 93. Completion rates were 73.2% in the paliperidone palmitate group and 66.0% in the RLAI group. The most common reason for discontinuation was lack of efficacy (9.9%) for the paliperidone palmitate group and withdrawal of consent and lack of efficacy (each 10.0%) for the RLAI group. Forty-three percent of paliperidone palmitate subjects and 50.0% of RLAI subjects received concomitant treatment with benzodiazepines for agitation, anxiety, or sleep disorders.

The mean (SD) modal doses for paliperidone palmitate and RLAI were 154.2 (11.9) mg and 27.1 (4.7) mg, respectively. Of note, the administration intervals differ for the two groups, as described in the Methods section of this article. Paliperidone palmitate is administered on day 1 and day 8 followed by monthly injections, while RLAI is administered biweekly from the first injection on day 8. Because of the release profile of RLAI and the study design, subjects in this group also received oral risperidone during the first 4 weeks and at the discretion of the investigator thereafter. The mean (SD) modal dose of oral risperidone in the RLAI group was 3.3 (1.6) mg/day through day 4, 3.7 (1.6) mg/day through day 15, 3.7 (1.6) mg/day through day 22, and 3.7 (1.7) mg/day through day 28. Also, 46 subjects received supplementation with oral risperidone in the RLAI group at week 5 (mean [SD] modal dose: 2.0 [0.7] mg/day), and 27 subjects at week 9 (mean [SD] modal dose: 1.8 [0.5] mg/day). Figure 2 shows comparable and therapeutic (>7.5 ng/mL) plasma levels of active drug throughout the study in both treatment groups.

Efficacy

Onset of Efficacy with Paliperidone Palmitate and Oral Risperidone (days 4, 15, and 22)

As stated previously, given the release profile of RLAI, the early time point data (days 4, 15, and 22) compare the ef-

| Table 1	Baseline Demographics, Clinical Characteristics, and Disposition	
Baseline Demographics and Clinical Characteristics	**Paliperidone Palmitate Group n=142**	**RLAI Group n=150**
Age, y, mean (SD)	39.9 (11.5)	39.5 (11.5)
Gender, n (%)		
Male	82 (57.8)	88 (58.7)
Female	60 (42.3)	62 (41.3)
Race, n (%)		
Caucasian	111 (78.2)	113 (75.3)
Black	17 (12.0)	25 (16.7)
Asian	14 (9.9)	12 (8.0)
Age at diagnosis, y, mean (SD)	26.2 (8.1)	27.4 (8.9)
Baseline PANSS total score, mean (SD)	93.3 (10.8)	93.3 (9.5)
Baseline CGI-S score, n (%)		
Marked (=5)	127 (89.4)	131 (87.3)
Severe (=6)	15 (10.6)	19 (12.7)
Baseline PSP score, mean (SD)	45.1 (10.2)	45.2 (11.1)
Disposition, n (%)		
Completed	104 (73.2)	99 (66.0)
Discontinued	38 (26.8)	51 (34.0)
Reasons for discontinuation		
Lack of efficacy	14 (9.9)	15 (10.0)
Withdrew consent	10 (7.0)	15 (10.0)
Adverse events*	7 (4.9)	6 (4.0)
Lost to follow-up	0 (0)	7 (4.7)
Other	7 (4.9)	8 (5.3)

*Adverse events leading to discontinuation for paliperidone palmitate were agitation in two subjects (1.4%) and the following events in one subject each (0.7%): schizophrenia exacerbation, suicidal ideation, vessel puncture site reaction, increased hepatic enzyme, and dystonia. AEs leading to discontinuation for RLAI were reported in one subject each (0.7%): suicide attempt, delirium, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood glucose, electrocardiogram change, abnormal hematology test results, and urinary tract infection (note that some subjects may have discontinued because of more than one AE).

fects of paliperidone palmitate with those of oral risperidone. Both groups showed a significant improvement from baseline in LS mean change (SE) in PANSS total score by the first post-baseline time point (day 4): paliperidone palmitate -5.0 (0.6), p<.001 and oral risperidone -3.4 (0.6), p<.001 (see Figure 3). Significant improvement continued in both groups at the following two time points: day 15 (-12.7 [1.2], p<.001 and -10.5 [1.2], p<.001, respectively); and day 22 (-17.0 [1.5], p<.001 and -15.3 [1.5], p<.001, respectively). Between-group differences were significant only at day 4 (p=.006).

LS mean change (SE) in CGI-S data was similar in that significant improvement versus baseline was observed by day 4 for both the paliperidone palmitate (-0.2 [0.05], p<.001) and oral risperidone (-0.1 [0.04], p<.001) groups, as well as at day 15 (-0.6 [0.08], p<.0001 and -0.6 [0.07], p<.0001, respectively) and at day 22 (-0.8 [0.09], p<.0001 and -0.8 [0.09], p<.0001, respectively). A significant improvement was observed in the distribution of the CGI-S scores at days 4, 15, and 22 for the paliperidone palmitate and oral risperidone groups (see Figure 4). Mean (SD) PSP scores also showed significant improvement at day 15 for both treatments (5.0 [1.0], p<.0001, for paliperidone palmitate and 5.7 [1.0], p<.0001, for oral risperidone). The responder rate (proportion of subjects with a 30% or greater reduction in PANSS total score) was

Figure 2 | **Plasma Levels of Paliperidone in the Paliperidone Palmitate Group and of Active Moiety in the RLAI Group**
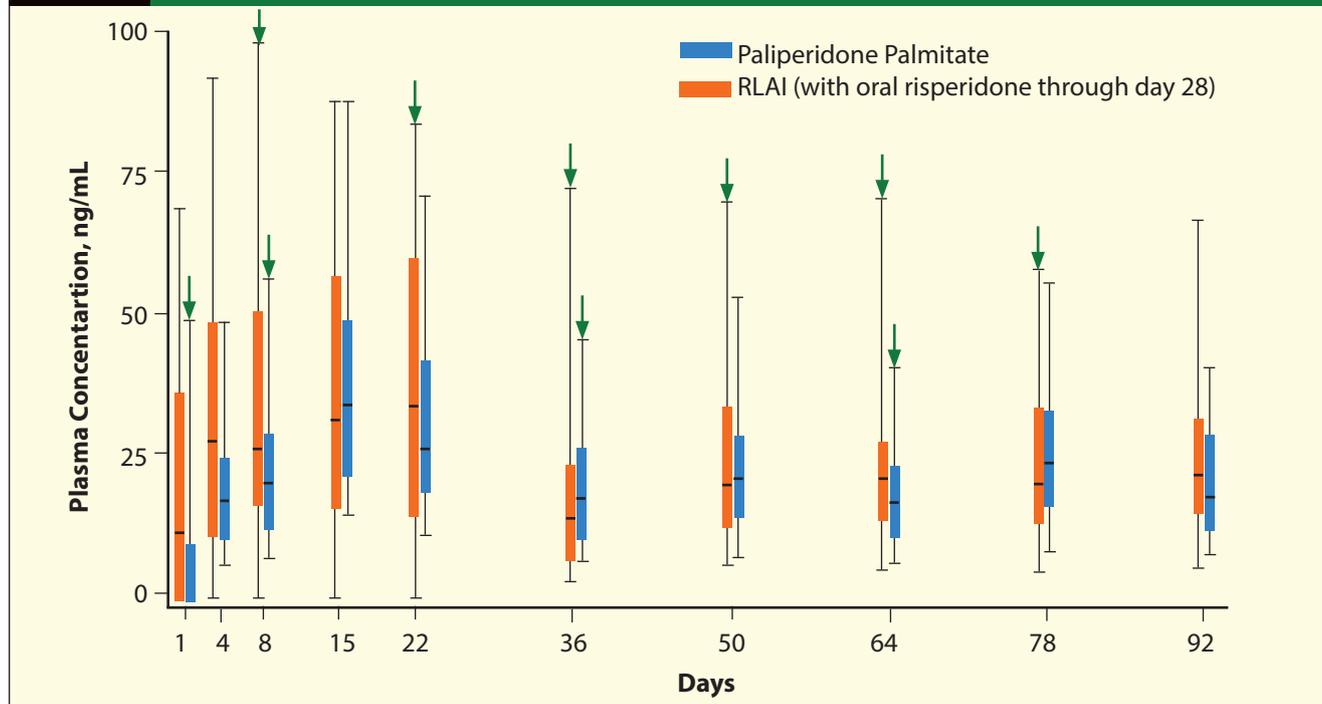
PK=pharmacokinetics; RLAI=risperidone long-acting injection. No formal PK analysis was conducted. Plasma level distributions are graphically presented as box-plots showing 25, 50, and 75 percentiles as boxes and 5 and 95 percentiles through the whiskers. Arrows (↓) denote days of injection of study drug for either the paliperidone palmitate or the RLAI treatment group. The paliperidone palmitate treatment group represents paliperidone level and the RLAI treatment group represents active moiety (sum of risperidone and paliperidone) levels.

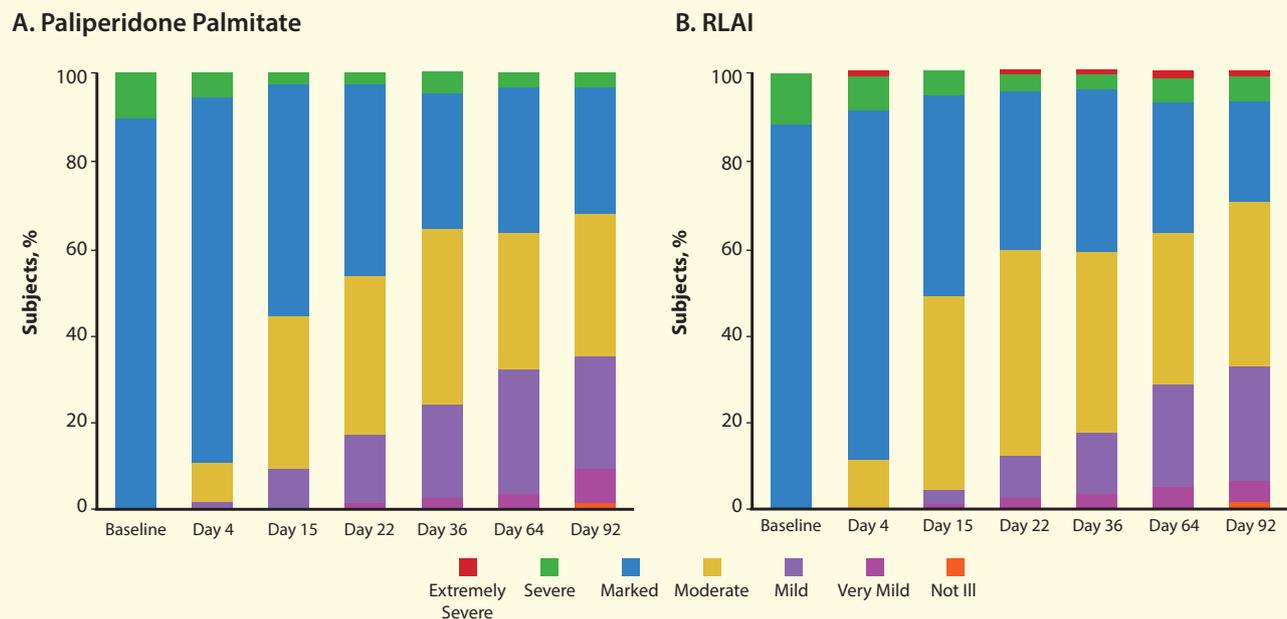**Figure 3** | **PANSS Total Score LS Mean Change from Baseline (LOCF Analysis)**
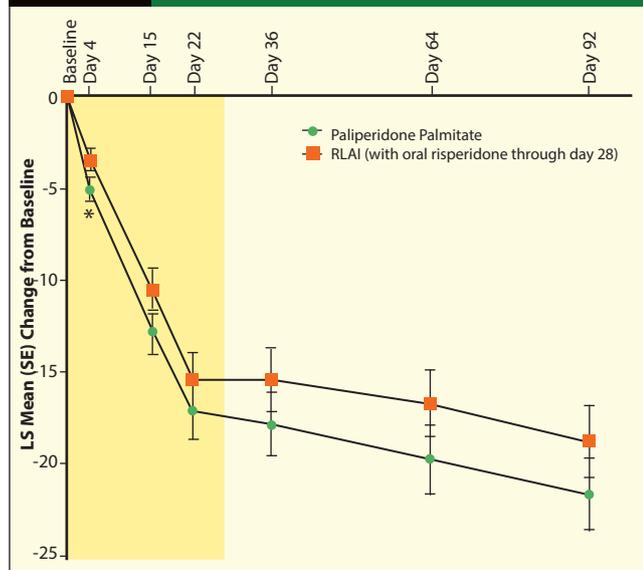
LOCF=last observation carried forward; LS=least-squares; RLAI= risperidone long-acting injection. Shaded areas correspond to the comparison of paliperidone palmitate with oral risperidone (for the RLAI group, supplementation with oral risperidone [1–6 mg] was required through day 28). Within-group differences from baseline were statistically significant at all time points. *p<.05 paliperidone palmitate versus RLAI.

not significantly different between the two groups at day 4 (see Figure 5) and was significantly greater with paliperidone palmitate than with oral risperidone at day 15 (26.1% versus 12.7%; p=.013) and day 22 (41.6% versus 32.0%; p=.048). Discontinuation rates with paliperidone palmitate and oral risperidone treatment during the early time periods were 0.0% and 0.7% for days 1 to 4; 4.9% and 10.0% for days 1 to 15; 7.0% and 13.3% for days 1 to 22.

### Efficacy at End Point with Paliperidone Palmitate and RLAI (week 13 [day 92])

LS mean change (SE) in PANSS total scores was significantly improved from baseline at end point (both p<.001) in the paliperidone palmitate (-21.5 [1.9]) and RLAI (-18.6 [1.9]) groups (see Figure 3). Using the noninferiority margin of the primary study (27), paliperidone palmitate demonstrated noninferiority to RLAI. Improvements were not statistically different for paliperidone palmitate and RLAI at end point for CGI-S score (-1.3 [0.1] versus -1.2 [0.1], p=.46) and PSP score (10.8 [1.5] versus 10.7 [1.5], p=.98). At end point, a significant improvement was observed in the distribution of CGI-S scores for both paliperidone palmitate and RLAI (see Figure 4). The responder rate at end point was 55.6% for paliperidone palmitate and 47.3% for RLAI (p=.073) (see Figure 5).

Figure 4 | **Categorical CGI-S Scores from Baseline to End Point for Paliperidone Palmitate (A) and RLAI (B) (LOCF Analysis)**

A. Paliperidone Palmitate

B. RLAI

Legend: Extremely Severe, Severe, Marked, Moderate, Mild, Very Mild, Not Ill

CGI-S=Clinical Global Impression-Severity; LOCF=last observation carried forward; RLAI=risperidone long-acting injection.
p<.001, from baseline to all time points for both the paliperidone palmitate and RLAI groups.

Figure 5 | **Percentage of Responders (LOCF Analysis)***

Legend: Paliperidone Palmitate, RLAI, Oral Risperidone
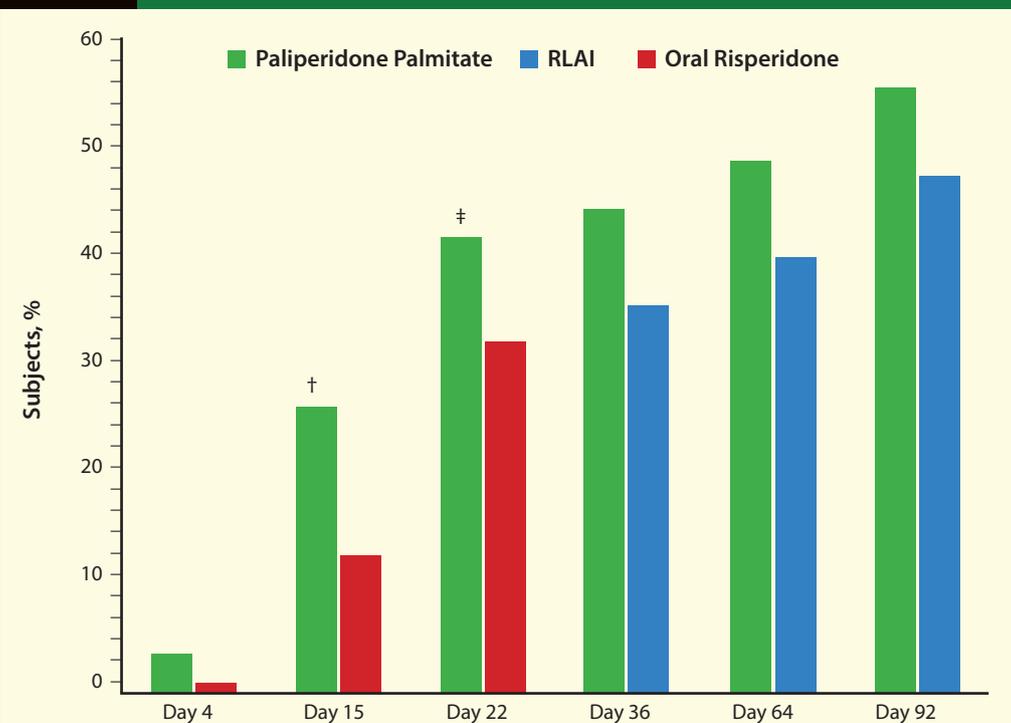
LOCF=last observation carried forward; PANSS=Positive and Negative Syndrome Scale; RLAI=risperidone long-acting injection. Hatched bars correspond to the comparison of paliperidone palmitate with oral risperidone (for RLAI group, supplementation with oral risperidone [1–6 mg] was required through day 28). *Response defined as a ≥30% improvement in PANSS total score; [†]p=.001, paliperidone palmitate versus RLAI; [‡]p=.048, paliperidone palmitate versus RLAI.

Table 2	Most Common Treatment-Emergent Adverse Events (≥5% in Either Group)	
	Subjects Reporting Adverse Event, n (%)	
	Paliperidone Palmitate n=142	**RLAI** n=150
Agitation	8 (5.6)	3 (2.0)
Akathisia	10 (7.0)	8 (5.3)
Headache	9 (6.3)	21 (14.0)
Injection site pain	8 (5.6)	2 (1.3)
Insomnia	15 (10.6)	16 (10.7)
Schizophrenia	12 (8.5)	8 (5.3)
Somnolence	11 (7.8)	2 (1.3)

Tolerability

At least one AE was reported by 71.1% of the paliperidone palmitate group and 64.7% of the RLAI group. The most common AEs (≥5% in either treatment group) were headache (paliperidone palmitate 6.3% versus RLAI 14.0%), insomnia (10.6% versus 10.7%), somnolence (7.8% versus 1.3%), akathisia (7.0% versus 5.3%), schizophrenia (8.5% versus 5.3%), agitation (5.6% versus 2.0%), and injection site pain (5.6% versus 1.3%) (see Table 2). Movement disorder-related measures included AE reports and rating scales. One or more movement disorder-related events were reported by 14.8% of paliperidone palmitate and 16.0% of RLAI subjects. The mean SAS, BARS, and AIMS scores were low (<1) in both groups throughout the study, with no significant between-group differences. Of subjects in the paliperidone palmitate group and subjects in the RLAI group, 15.5% and 11.3%, respectively, used extrapyramidal symptom medications during the study.

A total of 9.2% of paliperidone palmitate subjects and 6.0% of RLAI subjects had experienced serious AEs; the most common serious AEs were psychotic disorder and schizophrenia, which are considered part of the underlying medical condition.

Metabolic parameters were assessed by weight and laboratory values. The LS mean (SE) change in weight from baseline to end point was 1.0 (0.3) kg in the paliperidone palmitate group and 0.6 (0.3) kg in the RLAI group (p=.249). No significant between-group differences were observed for the mean change in plasma glucose, triglyceride, high-density lipoprotein, and low-density lipoprotein levels at end point.

Prolactin-associated measures include plasma levels and related AE reports. The LS mean (SE) change in prolactin levels (ng/mL) at end point was determined separately for females and males. For females in the paliperidone palmitate versus the RLAI group, LS mean (SE) changes were 17.6 (7.7) versus 0.4 (7.8), respectively (p=.081). For males, they were 17.7 (4.5) versus 9.6 (4.5), respectively (p=.120). Four subjects in the paliperidone palmitate group (three with amenorrhea, one with dysmenorrhea) and five in the RLAI group (three with amenorrhea, one with dysmenorrhea, one with ejaculation failure) reported an AE potentially related to prolactin elevation.

Discussion

This subgroup analysis of markedly-to-severely ill subjects with schizophrenia suggests that paliperidone palmitate administered once monthly after initiation injections (234 mg on day 1, followed by 156 mg 1 week later) improved symptoms as effectively as RLAI administered biweekly with oral risperidone supplementation for the first 3 weeks. The onset of efficacy as measured by significant improvements in efficacy scales was observed by day 4 in both groups, with significant improvements also noted through day 22. Of note, this finding was consistent with the PANSS rating of symptoms as well as the CGI-S rating of overall clinical status. Because of the release profile of RLAI, these first few weeks actually provide a comparison of the effect of paliperidone palmitate to that of oral risperidone up to the day 22 time point. There was no indication that paliperidone palmitate without oral supplementation might have a slower onset of efficacy than oral risperidone. In fact, the change in PANSS total score was greater at day 4 for the paliperidone palmitate group, with no significant between-group differences at subsequent time points in this 13-week study.

In addition, responder rates were similar or greater in the paliperidone palmitate versus the RLAI group at all time points. Again, this is especially notable at the early time points when the responder rate was higher with paliperidone palmitate versus oral risperidone (days 15 and 22). Thus, several measures suggest that paliperidone palmitate without oral antipsychotic supplementation can provide an early onset of efficacy similar to that of oral risperidone and to those reported for other oral antipsychotics (29-33). This finding and the plasma level data also confirm that the initiation regimens used in this study provide early and consistent therapeutic levels of drug (27).

Long-acting injectable agents are often viewed as appropriate for maintenance treatment in patients with stabilized schizophrenia. However, the finding of early efficacy onset is clinically relevant in that it also supports treatment initiation in non-stabilized, acutely symptomatic patients. Further, a rapid efficacy onset can simplify switching regimens when required.

The subgroup of subjects who are at least markedly ill at entry was chosen for this post hoc analysis because onset of efficacy may be a particularly important need for the patient population represented. This subgroup consisted of approximately one-third of the total ITT population of the

original study. Baseline demographics and disease-related characteristics did not reveal significant between-group differences in this subgroup. Also, as expected, baseline characteristics revealed that this was a subgroup with a relatively high PANSS total score (approximately 93) and low PSP score (approximately 45) compared with that seen in the overall study population (approximately 85 and 55, respectively) (27) (data on file, Johnson & Johnson Pharmaceutical Research and Development, LLC). The early onset of efficacy observed in this subgroup analysis was also seen in the overall study population, in which the PANSS total score improved significantly by day 4 in both paliperidone palmitate (mean [SD] -3.0 [5.5]) and RLAI groups (mean [SD] -2.3 [4.7]) (p<.001) for both comparisons versus baseline. There was also a small but significant between-group difference at day 4 only (LS mean -2.9 [0.3] and -2.3 [0.3], respectively [p=.039]) but not at any other time point through the 13-week end point (LS mean -14.9 [1.0] and -14.0 [1.0], respectively [p=.378]) (data on file, Johnson & Johnson Pharmaceutical Research and Development, LLC). It is relevant to note here that these agents have not been compared in a long-term maintenance trial to determine whether there are advantages to monthly versus biweekly injection regimen.

The most commonly reported AEs were generally similar in this subgroup compared with the overall study population (regardless of treatment group) (27), although there were some differences in the absolute rates. Because the RLAI group also included oral risperidone supplementation for the first 4 weeks and optionally thereafter, AE reports, weight, or laboratory changes due to oral risperidone versus RLAI could not be distinguished. However, no new tolerability signals were noted in either group.

The original study was not specifically designed to examine a particularly ill patient population; inclusion criteria of the study required a PANSS total score between 60 and 120, inclusive, at screening and baseline. However, in this post hoc analysis, only those subjects who were rated as markedly-to-severely ill by the CGI-S at study entry were included. Because most subjects were rated as markedly ill, the results presented here may not generalize to more severely ill populations. Also, it should be pointed out that the original study did not pre-specify an assessment of the onset of efficacy. This post hoc analysis evaluated onset by looking at the statistical significance of PANSS improvement from baseline in each group. A significant limitation here is the lack of a placebo group for comparison. It is well accepted that patients will experience some improvement simply by being in a clinical study; this was not controlled for in this study design. Also, the study did not prospectively define the onset of a clinically meaningful change. Thus, we used the 30% or greater improvement in PANSS total score as a generally acceptable measure of a

meaningful change (34). Finally, the study design had limited early time points that assessed efficacy, with day 4 as the first post-baseline efficacy measure.

In conclusion, in these markedly-to-severely ill subjects, onset of efficacy as measured by PANSS and CGI-S improvements was observed by day 4 (the first post-baseline efficacy assessment) in subjects receiving either paliperidone palmitate or oral risperidone through day 28. The findings also suggest that paliperidone palmitate alone improved symptoms at least as effectively as oral risperidone at day 4 through day 22, and as effectively as RLAI alone through end point, with no unexpected tolerability findings. The clinical advantages of the combined attributes of early onset of action with persistence of effect after the initiation regimen observed following paliperidone palmitate treatment without supplementation require further exploration. Results will provide additional guidance to clinicians who are considering the management of symptomatic patients with paliperidone palmitate relative to alternative approaches.

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