A Prospective Flexible-Dose Study of Paliperidone Palmitate in Nonacute But Symptomatic Patients With Schizophrenia Previously Unsuccessfully Treated With Oral Antipsychotic Agents

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ABSTRACT

Purpose: The goal of this study was to explore the tolerability, safety, and treatment response of flexible doses of once-monthly paliperidone palmitate (PP) in the subset of nonacute but symptomatic adult patients with schizophrenia previously unsuccessfully treated with oral antipsychotic agents in the PALMFlexS (Paliperidone Palmitate Flexible Dosing in Schizophrenia) study.

Methods: This was an interventional, single-arm, international, multicenter, unblinded, 6-month study performed in patients with schizophrenia. Patients were categorized according to reasons for switching. In patients switching because of lack of efficacy or for other reasons, primary efficacy outcomes were the proportion achieving treatment response (defined as ≥20% improvement in Positive and Negative Syndrome Scale [PANSS] total score from baseline to last-observation-carried-forward end point) and maintained efficacy (defined as noninferiority in the change in PANSS total score at end point versus baseline [Schuirmann's test]), respectively.

Findings: A total of 593 patients (intention-to-treat population) were enrolled: 63.1% were male; their mean (SD) age was 38.4 (11.8) years; and 78.6% had paranoid schizophrenia. The main reasons for transition to PP were patient's wish (n = 259 [43.7%]), lack of efficacy (n = 144 [24.3%]), lack of compliance (n = 138 [23.3%]), and lack of tolerability (n = 52 [8.8%]) with the previous oral antipsychotic medication. The recommended PP initiation regimen (150 milligram equivalents [mg eq] day 1 and 100 mg eq day 8) was administered in 93.9% of patients. Mean PANSS total score decreased from 71.5 (14.6) at baseline to 59.7 (18.1) at end point (mean change, −11.7 [15.9]; 95% CI, −13.0 to −10.5; $P < 0.0001$). Sixty-four percent of patients showed an improvement of ≥20% in PANSS total score, and the percentage of patients rated mildly ill or less in Clinical Global Impression–Severity increased from 31.8% to 63.2%. Mean personal and social performance total score (SD) increased (ie, improved) significantly for all patients from baseline to end point (58.1 [13.4] to 66.1 [15.7]; $P < 0.0001$).

Implications: The PALMFlexS study is a pragmatic interventional study compared with randomized controlled trials, conducted in a large, more representative sample of patients with schizophrenia, and designed specifically to mimic real-world clinical situations. The

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findings support the results from randomized controlled studies. They also demonstrate that a clinically relevant treatment response is possible in patients who are considered to be clinically stable by their physician, supporting the use of flexibly dosed PP in such patients. Clinical trials.gov number: NCT01281527. (*Clin Ther*. 2014;36:1372–1388) © 2014 The Authors. Published by Elsevier HS Journals, Inc.

Key words: long-acting antipsychotic, nonacute, paliperidone palmitate, schizophrenia.

INTRODUCTION

Schizophrenia is a complex and heterogeneous disorder with a range of symptoms that requires long-term treatment.[1] Continuous treatment is particularly important for patients with schizophrenia because disruption of long-term treatment increases the risk of relapse and hospitalization.[2]

Partial or nonadherence to antipsychotic treatment is the most important risk factor for relapse,[3] and intermittent therapy has proven inferior to continuous medication, in both recent-onset and multi-episode patients.[4,5] Although rates of nonadherence within a single month have been estimated at 40% to 50% after discharge following a first hospital admission,[6] several studies have shown that psychiatrists can often significantly overestimate the extent of adherence to oral medication.[7,8] This oversight is important because, among other reasons, it may contribute to the underutilization of long-acting injectable antipsychotic therapy (LAT).[6,9] In a separate study, patients with first-episode psychosis who had responded well in a 2-year open-label trial with risperidone long-acting injectable therapy[10] were followed up for an additional 3 years. Fifty percent of patients experienced a relapse within 15 weeks of treatment discontinuation, and nearly all patients (94%) relapsed within 2 years.[11] These data suggest that treatment interruption is directly linked to relapse even after long-term successful treatment, in turn contributing to the persistence of symptoms and loss of gains in functioning and quality of life.[12–16] Recent data also suggest that time in relapse is significantly associated with grey and white matter brain volume loss[17] and that consecutive relapses are highly correlated with progressive loss in brain volume.[18]

Relapse is very distressing to patients and caregivers[19] and imposes a significant financial burden on health care systems.[20] Furthermore, relapse fuels the progression of schizophrenia in a variety of ways, including stigma and loss of self-esteem.[21] Thus, the impact of partial or nonadherence to medication and subsequent relapse may drive the negative labeling of patients with schizophrenia and potentially lead to discrimination that can affect all aspects of a subject's life, including making or keeping friends and obtaining a job.[22] Nevertheless, patients often switch or discontinue antipsychotic therapy, most frequently due to lack of efficacy, adverse effects, or at their own discretion.[23–25]

Switching to LAT may improve adherence to treatment in patients with schizophrenia[26] due to the transparency of the medication delivery.[27] Partial or nonadherence in patients with schizophrenia is frequent and multifactorial (eg, due to lack of insight, lack of social support, negative symptoms, cognitive deficits, substance abuse). Therefore, greater confidence in the use of LAT could translate into broader and more effective use of these antipsychotic agents, as well as improved clinical outcomes.[9] LAT has been shown to significantly reduce relapse rates among patients with schizophrenia compared with those treated with oral antipsychotic agents,[28] although results of meta-analyses differ depending on the method used.[28–30] For instance, meta-analyses of randomized controlled trials have not consistently found differences.[28,29] A meta-analysis of mirror-image studies has shown superiority in favor of LAT versus oral antipsychotic agents in preventing hospitalization,[31] which most likely reflects that the comparative effectiveness of antipsychotic formulations is sensitive to research design. Indeed, mirror-image studies might be considered more capable of reflecting the relative impact of LAT compared with oral antipsychotic agents. However, it should be noted that mirror-image studies are not free from methodologic bias, due to the lack of randomization that can limit their value.[32] Data from a study investigating efficacy failure with paliperidone palmitate (PP) versus haloperidol decanoate in adult patients with schizophrenia or schizoaffective disorder, who were assessed as being at risk of relapse, have shown that the difference in the rate of efficacy failure was not statistically different for PP compared with haloperidol decanoate.[33]

PP is an atypical LAT designed for once-monthly intramuscular injection[34] that has been approved in the European Union,[35] the United States,[36] and >50 other countries worldwide, including Australia,

Canada, Japan, and the People's Republic of China. In the European Union, PP is indicated for the maintenance treatment of adult patients with schizophrenia. Three short-term pivotal studies have reported on the efficacy and safety of PP. [37–39] These studies used fixed doses, required an initial washout period before transition to PP from a previous oral antipsychotic agent, and were conducted in a well-defined, homogeneous, and otherwise healthy group of patients with schizophrenia. However, a more diverse population of patients with schizophrenia (eg, with higher rates of comorbidities, substance abuse, and/or comedications) is frequently seen in clinical practice. Thus, assessment of PP in a more representative setting is needed to obtain information and guidance on dose–response relationships and strategies for transition or switching directly from other antipsychotic treatments to PP.

The PALMFlexS (Paliperidone Palmitate Flexible Dosing in Schizophrenia) study is a pragmatic interventional study compared with randomized controlled trials, conducted in a large, more representative sample of patients with schizophrenia. It was specifically designed to mimic real-world clinical situations in which the transition to another antipsychotic is performed in stable, yet previously unsuccessfully treated, patients. The PALMFlexS study comprised samples from 3 distinct patient populations: patients with nonacute schizophrenia switching to PP from oral antipsychotic agents, nonacute patients switching to PP from LAT, and acutely ill patients switching to PP from oral antipsychotics. (The synopsis for the overall study is available at http://filehosting.pharmacm.com/DownloadService.ashx?client=CTR_JNJ_6051&studyid=229&filename=CR017215_CSR.pdf.) The primary objective for the group discussed in the present article was to explore the tolerability, safety, and treatment response of flexible doses of once-monthly PP in nonacute but symptomatic adult patients with schizophrenia previously unsuccessfully treated with oral antipsychotic agents.

PATIENTS AND METHODS

Study Design

This study was a prospective, interventional, single-arm, international, multicenter, unblinded, 6-month study performed in patients with schizophrenia. A total of 160 sites in 21 countries took part in the study (Austria, Belgium, Croatia, Denmark, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Lithuania, the Netherlands, Portugal, Spain, Sweden, Switzerland, Turkey, Ukraine, and the United Kingdom). Before trial initiation, the protocol was reviewed and approved by an independent ethics committee in all participating countries. The trial was performed in accordance with the Declaration of Helsinki and was consistent with the Good Clinical Practice of the International Conference on Harmonisation and applicable regulatory requirements. Before any trial-related activities commenced, patients provided their signed consent to participate in the trial after being informed of the nature and purpose of the study, participation/termination conditions, and the risks and benefits of treatment.

The study consisted of a 7-day screening and a 6-month prospective study period. The screening period included a $\geq$2-day oral tolerability test with paliperidone extended-release tablets for patients without source documentation of previous risperidone or paliperidone exposure. Only patients tolerating the drug, as judged by the treating physician, were eligible to enter the 6-month study period, the start of which was defined as the day of the first PP injection.

Patients

Eligible participants were male and female patients aged $\geq$18 years with a diagnosis of schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV]) who were switched to PP from an unsuccessful treatment with a previous oral antipsychotic agent. Patients were required to be in stable condition but symptomatic (ie, have been on the same oral antipsychotic given for the treatment of schizophrenia in an adequate therapeutic dose and with a change in Clinical Global Impression–Severity [CGI-S] score $\leq$1 in the 4 weeks before enrollment). Their current treatment was considered to have been unsuccessful due to 1 or more of the following: lack of efficacy (baseline Positive and Negative Syndrome Scale [PANSS] total score $\geq$70 or $\geq$2 items scoring $\geq$4 in the PANSS positive or negative subscale or $\geq$3 items scoring $\geq$4 in the PANSS general psychopathology subscale, as judged by the investigator), lack of tolerability or safety (the presence of clinically relevant adverse effects), lack of compliance, or the patient's wish. Patients were categorized according to the main reason for switching, either due to lack of efficacy or due to other reasons (lack of tolerability, lack of compliance, or patient's wish). The following criteria led to exclusion from study participation: psychiatric

diagnosis was due to direct pharmacologic effects of a substance or a general medical condition; antipsychotic treatment-naive; received clozapine during the last 3 months before the start of the study; considered to be at imminent risk of suicide even after clinical intervention; a history or current symptoms of tardive dyskinesia or neuroleptic malignant syndrome; pregnant or breastfeeding; or known allergies, hypersensitivity, or intolerance to risperidone or paliperidone or its excipients. Patients with current substance use or abuse, with the exception of intravenous drug use, were eligible for enrollment. There were no exclusions based on body mass index (BMI).

Treatment

PP was initiated at 150 milligram equivalents (mg eq) on day 1 and 100 mg eq on day 8 (±2 days) intramuscularly, both given in the deltoid muscle. Deltoid injections were to be alternated between the 2 deltoid muscles. At initiation of PP, patients were tapered off their previous oral antipsychotic, preferably within a maximum of 4 weeks, at the discretion of the treating physician. Subsequently, PP was administered once monthly in either the deltoid or gluteal muscle on days 38, 68, 98, 128, and 158 (±7 days) using flexible maintenance dosages within the range of 50 to 150 mg eq. Other than PP, no long-acting antipsychotic was allowed throughout the entire study. Psychotropic medications or other antipsychotic drugs given before study start for reasons other than the disease itself (eg, sleep induction or sedation) could be continued during the study at a stable dose. In case of worsening of psychotic symptoms between visits that required immediate intervention, oral antipsychotic medication (preferably paliperidone extended-release) could be given within the approved dose range. Benzodiazepines that were newly initiated during the study were allowed for rescue medication, preferably not for a period exceeding 10 consecutive days. Benztropine mesylate or biperiden up to 4 mg/d (or its equivalent if benztropine mesylate was not locally available) or trihexyphenidyl up to 10 mg/d could be used for the treatment of extrapyramidal motor symptoms (EPMS). The need for benzodiazepines and anticholinergic medication had to be re-evaluated on an ongoing basis.

Efficacy Assessments

The primary efficacy outcome for nonacute patients switched from previous oral antipsychotic medication due to lack of efficacy was the percentage of patients achieving treatment response, defined as ≥20% improvement in PANSS total score from baseline (day 1) to last-observation-carried-forward (LOCF) end point (at 6 months or early discontinuation). Improved efficacy of ≥20% was specified as the primary end point in this group of patients, as they were considered stable by their treating physician for at least 1 month before enrollment while being prescribed an adequate dose of a highly potent antipsychotic drug; therefore, their improvement would not be expected to be comparable to what generally would be observed in acutely ill patients in whom ≥30% or ≥50% improvements are considered more adequate. The PANSS was completed by trained and qualified raters who were aware that the patient was receiving PP in the setting of a clinical study. All PANSS raters completed a study-specific rater training and qualification program. Each rater was required to meet the standard of 80% concordance with the acceptable scores or score ranges for the videotaped interview. For patients switching for other reasons, the primary efficacy outcome was maintained efficacy from baseline to end point, defined as noninferiority in the change in PANSS total score at end point versus baseline, as measured by using Schuirmann's test. Actual values and changes from baseline (day 1) in PANSS total score and CGI-S scale score (on a range from 1 [not ill] to 7 [extremely ill]) were analyzed. Clinical Global Impression–Change scores were also recorded, and relative frequency distributions were calculated for CGI-S and CGI-Change scores.

Secondary outcomes encompassed actual values and changes from baseline in PANSS total score, PANSS sub scale scores, and PANSS Marder factor scores[40] (positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement and anxiety/depression), Personal and Social Performance (PSP) total score, PSP domain scores[41] (socially useful activities including work and studies, personal and social relationships, self-care, disturbing and aggressive behaviors, each rated on a 6-point scale (ranging from 0 [absent] to 5 [very severe]), by converting to a score ranging from 1–100). Also evaluated were actual values and changes from baseline in subjective well-being (assessed by using the Subjective Well-being under Neuroleptics Scale according to a 6-point Likert scale ranging from 1 [not at all] to 6 [very much] with 5 subscores [mental

functioning, social integration, emotional regulation, physical functioning, and self-control] and a total score),[42] treatment satisfaction (assessed in patients by using the 14-item Treatment Satisfaction Questionnaire for Medication scale and physician treatment satisfaction by using a 7-point categorical scale), sleep and daytime drowsiness (evaluated by using an 11-point categorical rating scale),[43] and caregiver burden (evaluated by using the Involvement Evaluation Questionnaire)[44] in patients with a caregiver and depending on the availability of the scale in the local language. Assessment of abilities/capabilities deemed critical for social reintegration and functioning was conducted by using the Mini–International Classification of Functionality, Disability and Health Rating for Activity and Participation Disorders in Psychological Illnesses (Mini-ICF-APP) scale[45–47] and summarized descriptively at each assessment point including LOCF end point (Mini-ICF-APP scale items may be used to evaluate patient's capabilities in clinical routine). Each dimension was rated on a Likert scale ranging from 0 (no disability) to 4 (total disability).

Tolerability and Safety

EPMS were assessed by using the Extrapyramidal Symptom Rating Scale.[48] Weight was recorded at each assessment point (including LOCF end point), and BMI was calculated. All treatment-emergent adverse events (TEAEs), defined as AEs that were new in onset or were aggravated in severity after initiation of PP, were documented and coded by using the Medical Dictionary for Regulatory Activities (version 13.0).

Data Analysis

For patients switching due to lack of efficacy, the proportion with at least 20% improvement in PANSS total score was expected to be 30%. Using the large sample normal approximation, it was estimated that at least 81 patients were required to reach a 95% CI for a single proportion that maximally extends 10% from the observed proportion. For patients switching for other reasons, a mean difference of 5 points between baseline and end point on the PANSS total score was considered to be a minimum clinically relevant difference for maintained efficacy. Using Schuirmann's test, it was estimated that 124 patients were required to test for noninferiority, assuming a SD of 17 points, a power of 90%, and a 1-sided significance level of 0.025. A sample size of ~600 patients was chosen to explore additional subgroups such as the different oral antipsychotic from which patients were switched and recently diagnosed versus more chronic patients; this sample size would also account for patients with no analyzable data.

The intention-to-treat (ITT) population comprised all patients who received PP at least once. The efficacy analysis population included all ITT patients with at least 1 postbaseline assessment on any efficacy parameter. Treatment response analyses were performed on the efficacy ITT population.

End point analysis using the LOCF method was performed in addition to observed case analysis. Actual values and changes from baseline were summarized descriptively at each assessment time point and at the patient's last evaluation (LOCF end point), and categorical variables were summarized with frequency and percentage. Safety and tolerability were evaluated throughout the study on the safety ITT population, which comprised all ITT patients who had at least 1 postbaseline observation on any safety parameter. On the level of all reported TEAEs, frequency distributions that were calculated included severity of the events (ie, mild, moderate, severe) and causal relationship to treatment (ie, not related, doubtful, possible, probable, very likely).

Quantitative differences between subgroups according to reason for switching were also tested by means of the Wilcoxon 2-sample test.

RESULTS

Demographic Characteristics and Patient Disposition

Overall, the ITT population consisted of 593 nonacute but symptomatic patients switched from oral antipsychotic agents who received at least 1 dose of PP during the study. Patient disposition is described in Figure 1. The main reasons for transition to PP were patient's wish (n = 259 [43.7%]), lack of efficacy (n = 144 [24.3%]), lack of compliance (n = 138 [23.3%]), and lack of tolerability (n = 52 [8.8%]) with the previous oral antipsychotic medication. A total of 442 (74.5%) patients completed the study. The proportion of patients completing the study, as well as the main reasons for withdrawal, was similar across subgroups by reason for switching: 72.9% (n = 105) for patients switching due to lack of efficacy and 75.1% (n = 337)

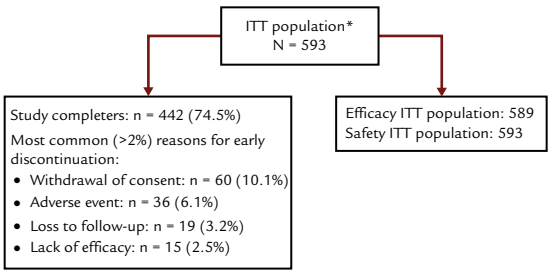


Figure 1. Patient disposition. *Patients who received at least one dose of study drug. ITT = intention-to-treat.

for patients switching for other reasons. The main reasons for early study discontinuation for all patients were withdrawal of consent (n = 60 [10.1%]), an AE (n = 36 [6.1%]), loss to follow-up (n = 19 [3.2%]), and lack of efficacy (n = 15 [2.5%]).

The majority of patients were male (63.1%) and had a diagnosis of paranoid schizophrenia (78.6%) (Table I). Most (n = 360 [60.7%]) patients had been previously hospitalized at least twice. At baseline, patients had a mean (SD) PANSS total score of 71.5 (14.6) and a mean baseline CGI-S score of 3.9 (0.9). Overall, 363 patients (61.2%) had at least 1 comorbidity at baseline, and 382 patients (64.4%) were treated with at least 1 concomitant medication before the study. The most frequently reported previous antipsychotic medications are presented in Table II. At baseline, 47 patients (9.0%) were reported to have some kind of substance abuse (with or without impairment).

After the day 1/day 8 initiation regimen, the PP mean modal maintenance dose for all patients was 101.4 (33.4) mg eq (Table I). Nearly all (n = 557 [93.9%]) patients received PP according to the recommended regimen on day 1 (150 mg eq) and day 8 (100 mg eq). The mean modal maintenance dose was higher for patients switching for lack of efficacy than those switching for other reasons; for example, a higher proportion of patients switching for lack of efficacy received 150 mg eq as the third dose. Approximately one half of patients (n = 287 [48.4%]) had 1 dosage adjustment during the study; 14.5% (n = 86) had 2 dose adjustments and 9.9% (n = 59) >2 dose adjustments (which included any dose changes made after administration of the third dose). The most common reason for maintenance dose adjustment was insufficient efficacy (n = 198 [33.4%]). Most dose adjustments were dose reductions (57.8%) rather than dose increases (42.2%).

Efficacy Outcomes

In total, 61.5% of patients who switched for lack of efficacy showed an improvement of ≥20% in mean PANSS total score at LOCF end point (Table III). Efficacy was maintained (ie, change in PANSS total score at end point vs baseline was not inferior as measured by using Schuirmann's test, $P < 0.0001$) in patients who switched for reasons other than lack of efficacy. In this group, 64.8% of patients had an improvement of ≥20% in PANSS total score at LOCF end point.

The baseline mean PANSS total score was 11.7 points higher for patients who switched due to lack of efficacy compared with those who switched for other reasons (Table IV). Mean PANSS total score significantly improved (baseline to LOCF end point, $P < 0.0001$) for the total ITT efficacy population, including those who switched due to lack of efficacy and those who switched for other reasons (Figure 2).

The PANSS subscale and factor scores at baseline were statistically significantly higher ($P < 0.0001$) on Wilcoxon 2-sample testing in patients switched for efficacy reasons compared with patients switched for other reasons. The change in mean PANSS total score was similar for patients switching due to lack of efficacy or for other reasons (mean [SD] change of –12.1 [15.1] and –11.6 [16.2], $P = 0.8252$ [baseline to LOCF end point], respectively). There was a statistically significant ($P < 0.0001$ [baseline to LOCF end point]) decrease (ie, improvement) for all patients in all PANSS subscale (Table IV) and PANSS Marder factor scores (see Supplemental Table in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.08.014).

The CGI-S scale score for all patients improved significantly (mean [SD] decrease, –0.6 [1.0]; $P < 0.0001$ [baseline and LOCF end point]) (Table IV). The change in mean CGI-S scale score was similar for patients switching due to lack of efficacy or for other reasons (mean [SD] changes of –0.6 [0.9] and –0.6 [1.1], $P = 0.7621$ [baseline to LOCF end point; Wilcoxon 2-sample test]). The proportion of all patients rated mildly or less ill based on the CGI-S scale score increased from 31.8% (n = 186) at

Table I. Patient baseline demographic characteristics and dosing information (intention-to-treat population).

Characteristic	Total (N = 593)	Switched for Lack of Efficacy (n = 144)	Switched for Other Reasons (n = 449)
Age, y[*]	38.4 (11.8)	39.8 (12.2)	38.0 (11.7)
Sex, %			
Male	63.1	61.1	63.7
Female	36.9	38.9	36.3
Schizophrenia diagnosis, no. (%)			
Paranoid	466 (78.6)	114 (79.2)	352 (78.4)
Disorganized	43 (7.3)	7 (4.9)	36 (8.0)
Catatonic	5 (0.8)	1 (0.7)	4 (0.9)
Undifferentiated	54 (9.1)	15 (10.4)	39 (8.7)
Residual	25 (4.2)	7 (4.9)	18 (4.0)
Years since first psychotic symptoms[*]	12.1 (9.6)	12.8 (10.0)	11.9 (9.4)
Weight, kg[*]	81.0 (17.7)	80.7 (17.1)	81.1 (17.9)
Body mass index, kg/m^2[*]	27.6 (5.9)	27.8 (6.2)	27.6 (5.8)
Patients with ≥1 comorbidity, no. (%)[†]	363 (61.2)	86 (59.7)	277 (61.7)
Body systems for which patients (≥5%) report ≥1 comorbidity			
Psychiatric disorders	131 (22.1)		
Metabolism and nutrition disorders	91 (15.3)		
Nervous system disorders	83 (14.0)		
Vascular disorders	52 (8.8)		
Gastrointestinal disorders	51 (8.6)		
Respiratory, thoracic, and mediastinal disorders	44 (7.4)		
Infections and infestations	36 (6.1)		
Musculoskeletal and connective tissue disorders	35 (5.9)		
No. (%) of patients with previous hospitalizations			
None	113 (19.1)	21 (14.6)	92 (20.5)
1	120 (20.2)	30 (20.8)	90 (20.0)
≥2	360 (60.7)	93 (64.6)	267 (59.5)
PP dosing			
No. (%) of patients receiving PP initiation regimen at day 1 and day 8 according to protocol[‡]	557 (93.9)	137 (95.1)	420 (93.5)
Modal PP maintenance dose, mg eq[*,§]	101.4 (33.4)	106.3 (33.7)	99.8 (33.2)
Last PP maintenance dose received (n = 541), no. (%)			
50 mg eq	52 (9.6)	8 (6.1)	44 (10.7)
75 mg eq	168 (31.1)	33 (25.2)	135 (32.9)
100 mg eq	172 (31.8)	44 (33.6)	128 (31.2)
150 mg eq	149 (27.5)	46 (35.1)	103 (25.1)
Relevant comedications			
No. (%) of patients using benzodiazepines			
At baseline	138 (23.3)	35 (24.3)	103 (22.9)
Newly initiated during study	125 (21.1)	24 (16.7)	101 (22.5)
At LOCF end point	123 (20.7)	27 (18.8)	96 (21.4)

(continued)

Table I. (continued).

Characteristic	Total (N = 593)	Switched for Lack of Efficacy (n = 144)	Switched for Other Reasons (n = 449)
At 6 months for completers[¶]	85 (19.2)	23 (21.9)	62 (18.4)
No. (%) of patients using anticholinergics			
At baseline	67 (11.3)	22 (15.3)	45 (10.0)
Newly initiated during study	48 (8.1)	14 (9.7)	34 (7.6)
At LOCF end point	46 (7.8)	16 (11.1)	30 (6.7)
At 6 months for completers[¶]	31 (7.0)	11 (10.5)	20 (5.9)

LOCF = last-observation-carried-forward; mg eq = milligram equivalents; PANSS = Positive and Negative Syndrome Scale; PP = paliperidone palmitate.
[*]Mean (SD).
[†]Individual patients can be labeled for >1 comorbidity.
[‡]The recommended initiation regimen was PP 150 mg eq on day 1 and 100 mg eq on day 8 given in the deltoid muscle.
[§]Excluding the initiation regimen (day 1/day 8).
[¶]Total, n = 442; switched for lack of efficacy, n = 105; switched for other reasons, n = 337.

baseline to 63.2% (n = 370) at LOCF end point (Figure 3).

Measures of patients' Subjective Well-being under the Neuroleptics Scale score, and patient's satisfaction with medication (Treatment Satisfaction Questionnaire for Medication global satisfaction score), sleep quality, and daytime drowsiness also showed clinically relevant and statistically significant improvements

Table II. Ten most frequent previous oral antipsychotic medications before switching to paliperidone palmitate at baseline.*

	Reported Daily Dose (mg)		Reported Duration[†] (d)	
Antipsychotic	No. of Patients	Mean (SD) Daily Dose (mg)	No. of Patients	Mean (SD) Duration of Prior Use (d)
Risperidone	206	4.3 (2.3)	33	257.6 (468.4)
Paliperidone ER	116	7.6 (2.8)	26	118.4 (161.4)
Olanzapine	101	15.4 (8.1)	30	191.9 (281.7)
Aripiprazole	65	21.8 (11.4)	21	262.9 (318.5)
Quetiapine	39	438.5 (271.8)	10	222.0 (257.7)
Haloperidol	37	10.6 (8.3)	13	456.5 (517.1)
Amisulpride	29	503.5 (287.2)	7	420.6 (584.5)
Quetiapine fumarate	26	450.2 (285.3)	5	371.0 (466.4)
Sertindole	7	9.1 (5.0)	1	69.0 (-)
Ziprasidone	5	128.0 (85.6)	2	116.5 (112.4)

ER = extended-release.
[*]For 591 patients, the switch medication and the dose were known.
[†]The duration of use of switch medication was not available for all patients.

Table III. Proportion of patients with improvement in Positive and Negative Syndrome Scale total score (%) at last-observation-carried-forward end point.

Improvement	Total Population (%) (n = 589)	Patient Switched For: Lack of Efficacy (%) (n = 143)	Other Reasons (%) (n = 446)
≥20% improvement (95% CI)	64.0 (60–68)	61.5 (53–69)	64.8 (60–69)
≥30% improvement (95% CI)	51.4 (47–55)	39.9 (32–48)	55.2 (51–60)
≥50% improvement (95% CI)	30.4 (27–34)	16.8 (12–24)	34.8 (30–39)

($P < 0.0001$ for all values [baseline to LOCF end point]) (Table IV). There were no significant differences for these parameters between subgroups based on reason for switching. There was also a statistically significant improvement in physicians' satisfaction scores for all aspects of treatment (efficacy, safety, mode of administration, and overall satisfaction; all, $P < 0.0001$ [baseline to LOCF end point]).

Functioning Outcomes

The mean (SD) PSP total score increased (ie, improved) significantly for all patients (58.1 [13.4] to 66.1 [15.7], $P < 0.0001$ [baseline to LOCF end point]). Baseline functioning in PSP was statistically significantly higher in patients switched for other reasons (59.0 [13.6]) compared with patients switched for efficacy reasons (55.3 [12.3]; $P < 0.01$ [baseline to LOCF end point], Wilcoxon 2-sample testing), as was the change in PSP total score (8.8 [14.4] vs 5.5 [12.3], respectively; $P < 0.05$ [baseline to LOCF end point]). Improvement in patient functioning was also reflected in the distribution of PSP total scores (Figure 4A) and in the distribution in categories of functional impairment for selected PSP domains (Figure 4B).

Illness-related disabilities in activity and participation also improved significantly (19.8 [7.9] to 15.9 [8.8]; $P < 0.0001$ [baseline to LOCF end point]) according to Mini-ICF-APP total scores. Statistically significant improvements were observed across all domains of activity and participation as measured by using the Mini-ICF-APP (all P values < 0.0001) (Figure 5).

Tolerability and Safety

During the study, 59.7% (n = 354) of patients experienced at least 1 TEAE. Most TEAEs (93.1%) were rated as mild or moderate in intensity. TEAEs occurring in ≥5% of patients were injection site pain (n = 73 [12.3%]), insomnia (n = 51 [8.6%]), anxiety (n = 40 [6.7%]), psychotic disorder (n = 36 [6.1%]), and headache (n = 33 [5.6%]) (Table V). The majority (75.8%) of TEAEs resulted in no change in dosage.

Eighteen (3.0%) patients reported at least 1 potentially prolactin-related TEAE, 4 (0.7%) patients reported hyperprolactinemia, and 7 (1.2%) patients reported a potentially prolactin-related TEAE as well as hyperprolactinemia. There were no obligatory protocol-based laboratory tests during this pragmatic study. The mean Extrapyramidal Symptom Rating Scale total score at baseline was 2.8 in the whole group, indicating low levels of EPMS. Nevertheless, there was a statistically significant reduction in Extrapyramidal Symptom Rating Scale total score (2.8 [5.0] to 1.6 [3.8], $P < 0.0001$ [baseline to LOCF end point]). The proportion of patients who received anticholinergic agents had a reduction from baseline to end point in both subgroups (Table I). There was a mean (SD) increase of 0.4 (1.8) kg/m^2 (95% CI, 0.3–0.6) in BMI and a mean weight change between baseline and end point of 1.2 (5.0) kg (95% CI, 0.7–1.6) in the whole group. In total, 81 (15.4%) patients had a ≥7% increase in weight from baseline to LOCF end point.

Overall, 42 (7.1%) patients reported ≥1 AE that led to early termination of the study. Two deaths (completed suicides) occurred during the study; both were male subjects (26 and 31 years old). These deaths were considered by the investigator as not related and doubtfully related, respectively, to the study drug.

The proportion of patients with substance abuse, which was low at baseline (9.0%), decreased to 6.9% at LOCF end point.

Table IV. Secondary outcomes.*

Outcome	Baseline (Mean [SD])	LOCF End Point (Mean [SD])	Mean (SD) Change From Baseline to LOCF End Point	95% CI	P†
Mean PANSS total score					
All patients (n = 589)	71.5 (14.6)	59.7 (18.1)	−11.7 (15.9)	−13.0 to −10.5	<0.0001
Patients switched for lack of efficacy (n = 143)	80.3 (11.3)	68.2 (17.0)	−12.1 (15.1)	−14.6 to −9.6	<0.0001
Patients switched for other reasons (n = 446)	68.6 (14.4)	57.0 (17.6)	−11.6 (16.2)	−13.1 to −10.1	<0.0001
Mean PANSS Positive Subscale					
All patients (n = 589)	15.5 (4.9)	12.7 (5.1)	−2.8 (4.9)	−3.2 to −2.4	<0.0001
Patients switched for lack of efficacy (n = 143)	17.1 (4.2)	14.5 (5.4)	−2.6 (5.0)	−3.6 to −1.8	<0.0001
Patients switched for other reasons (n = 446)	15.0 (5.0)	12.1 (4.9)	−2.9 (4.9)	−3.3 to −2.4	<0.0001
Mean PANSS Negative Subscale					
All patients(n = 589)	20.2 (5.4)	16.7 (5.9)	−3.5 (5.4)	−3.9 to −3.0	<0.0001
Patients switched for lack of efficacy (n = 143)	23.1 (4.9)	19.5 (5.4)	−3.6 (4.9)	−4.4 to −2.8	<0.0001
Patients switched for other reasons (n = 446)	19.3 (5.2)	15.8 (5.7)	−3.5 (5.5)	−4.0 to −2.9	<0.0001
Mean PANSS General Psychopathology Subscale					
All patients (n = 589)	35.8 (8.0)	30.3 (9.2)	−5.5 (8.4)	−7.3 to −4.6	<0.0001
Patients switched for lack of efficacy (n = 143)	40.1 (6.7)	34.1 (8.8)	−6.0 (8.1)	−6.1 to −4.5	<0.0001
Patients switched for other reasons (n = 446)	34.4 (7.9)	29.1 (9.0)	−5.3 (8.5)	−6.1 to −4.8	<0.0001
CGI-S Score					
All patients (n = 585)	3.9 (0.9)	3.3 (1.1)	−0.6 (1.0)	−0.7 to −0.5	<0.0001
SWN-S total Score					
All patients (n = 521)	80.1 (17.2)	85.5 (17.3)	5.4 (15.7)	4.0 to 6.7	<0.0001
TSQM global satisfaction score					
All patients (n = 494)	55.9 (21.5)	65.0 (25.1)	9.1 (29.0)	6.6 to 11.7	<0.0001
Quality of sleep score‡					
All patients (n = 582)	6.8 (2.6)	7.3 (2.4)	0.5 (2.8)	0.3 to 0.7	<0.0001
Drowsiness score§					
All patients (n = 582)	3.9 (2.9)	3.1 (2.8)	−0.9 (3.4)	−1.1 to −0.6	<0.0001

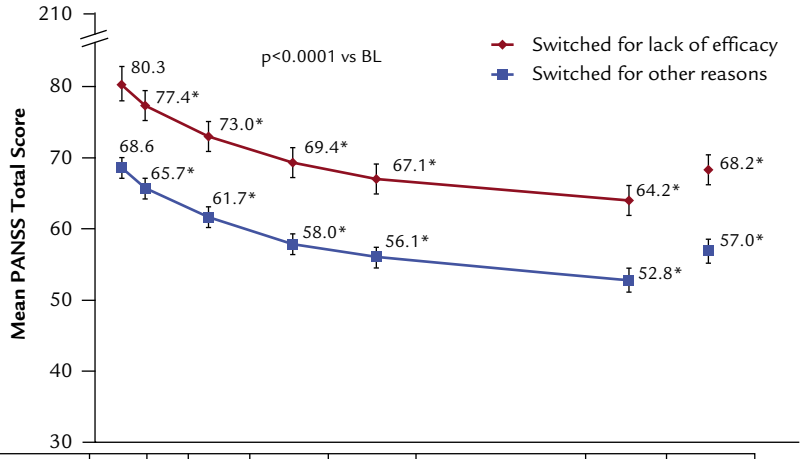
CGI-S = Clinical Global Impression–Severity; LOCF = last-observation-carried-forward; PANSS = Positive and Negative Syndrome Scale; SWN-S = Subjective Well-being under Neuroleptics Scale; TSQM = Treatment Satisfaction Questionnaire for Medication.

*Only patients with a valid baseline measurement and at least 1 valid follow-up assessment were included.

†Within-group difference was tested by using the Wilcoxon signed-rank test.

‡A higher score indicates improvements in the quality of sleep.

§A lower score indicates improvements in the level of drowsiness.



No. of patients switched to PP due to:	Day 1 (BL)	Day 8	Month 1	Month 2	Month 3		Month 6	LOCF End Point
Lack of efficacy	143	143	137	127	117		103	143
Other reasons	446	444	425	399	383		335	446

Figure 2. Change in mean Positive and Negative Syndrome Scale (PANSS) total score over time. Error bars represent 95% CIs. LOCF = last-observation-carried-forward; PP = paliperidone palmitate. *$P <$ 0.0001 versus baseline (BL).

DISCUSSION

Data from the present study support results provided by previous fixed-dose, randomized controlled clinical trials in which the efficacy of PP in the treatment of schizophrenia has been demonstrated. Furthermore, our findings expand on results from studies in stabilized patients with schizophrenia, which demonstrated greater improvements in clinical symptoms and functioning when switched to an LAT.[49–51] It should be considered that injectable therapy may indirectly influence the observed efficacy benefits of treatment with PP due to the increased interaction with health care professionals that may occur when administering LAT. However, the design of the present study does provide clinical experience of longer-term treatment with PP, drawing on the clinical judgment of efficacy and tolerability of the investigating physicians to access the most appropriate dose of PP that a patient receives.

Pragmatic studies are considered relevant because they add to the different levels of evidence available regarding treatments,[28,31] and by examining the effect size of the change, rather than the question of whether there has been improvement, helps to put the data into perspective. In this study, nonacute but symptomatic patients with schizophrenia switched to flexibly dosed

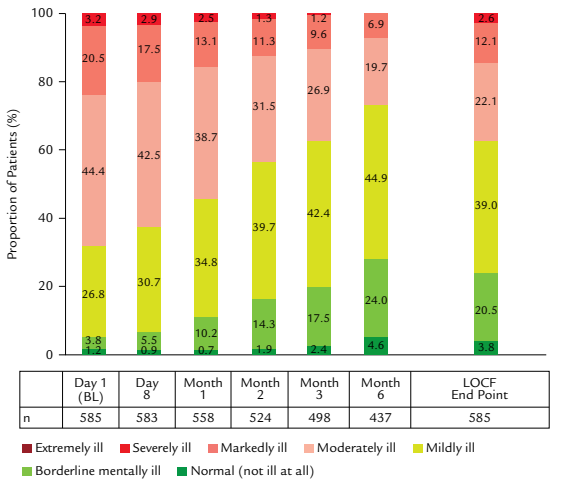


Figure 3. Clinical Global Impression–Severity score over time. BL = baseline; LOCF = last-observation-carried-forward.

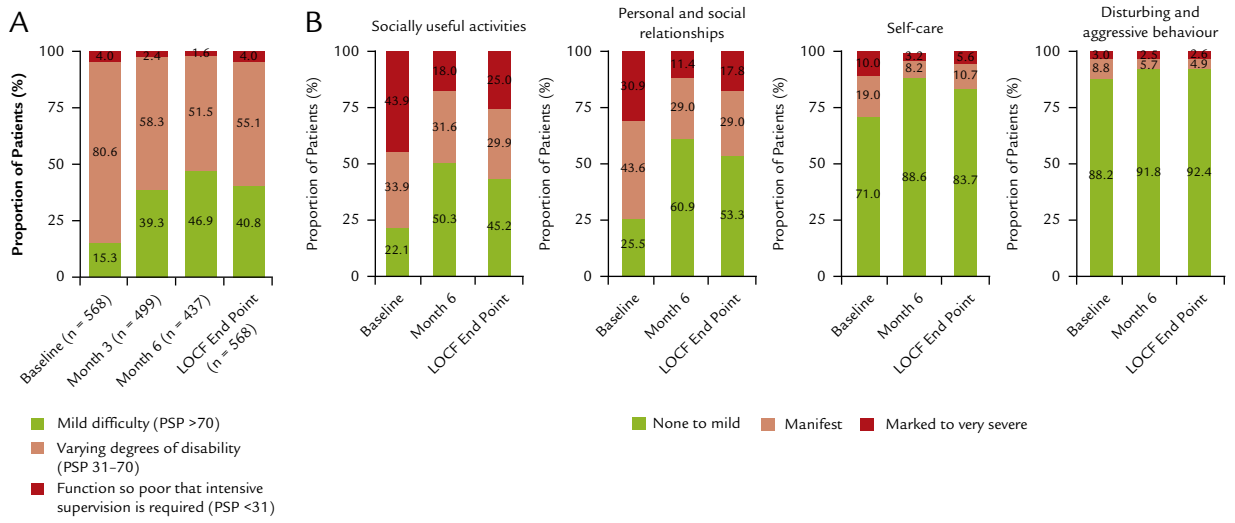


Figure 4. (A) Frequency distribution of Personal and Social Performance (PSP) total score over time and (B) frequency distribution of functioning for selected PSP domains at baseline and last-observation-carried-forward (LOCF) end point.

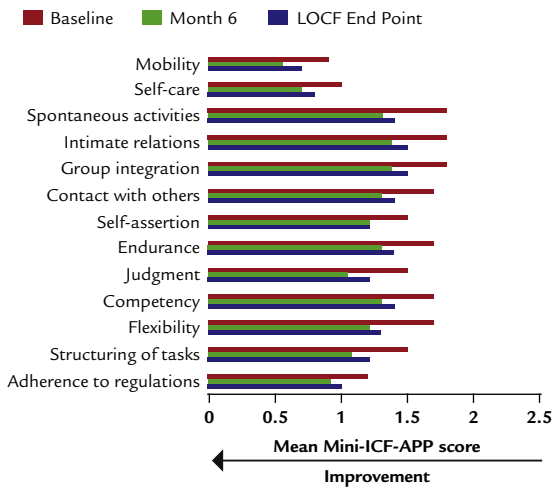


Figure 5. Mean Mini International Classification of Functionality, Disability and Health (ICF) Rating for Activity and Participation Disorders in Psychological Illnesses (Mini-ICF-APP) domain scores at baseline and last-observation-carried-forward (LOCF) end point. Change from baseline to month LOCF $P < 0.0001$ for all domains.

PP from their previous unsuccessful oral antipsychotic medication reported significant and clinically relevant improvements in clinical symptoms, disease severity, psychosocial functioning, and relevant ability domains of activation and participation comparable to the effects seen in randomized controlled clinical trials. However, contrary to most randomized controlled clinical trials, the pragmatic and flexible dose design of this study allowed treating physicians to adjust and optimize antipsychotic treatment with PP based on patients' individual needs, which more closely resembles clinical practice. A further advantage is that patient continuation with treatment is potentially

Table V. Treatment-emergent adverse events experienced by ≥5% of patients (safety, intention-to-treat population).

Event	No. (%) of Patients
Injection site pain	73 (12.3)
Insomnia	51 (8.6)
Anxiety	40 (6.7)
Psychotic disorder	36 (6.1)
Headache	33 (5.6)

longer than achievable otherwise, and it may provide more meaningful longer-term data over the duration of the study. Patients in this study were nonacute but symptomatic and considered as stable by their treating physician for at least 1 month before enrollment, and the majority showed a further clinically relevant improvement of their clinical symptoms. Even more, approximately one third of patients (30.4%) achieved a $\geq$50% improvement in PANSS total score regardless of their reason for switching. Thus, a considerable proportion of those patients achieved an improvement of comparable magnitude to acutely ill patients previously treated with oral antipsychotic agents in a 6-month study (PALMFlexS; Schreiner/Hargarter et al: acute patients switched from oral antipsychotics [manuscript in preparation]). This result is of particular clinical relevance because it demonstrates that switching patients who are considered clinically stable still offers the opportunity to experience some further improvement in a clinically relevant symptom (including negative symptoms). This improvement also applies to patients switched for reasons other than lack of efficacy with the previous oral antipsychotic agent. Psychotic symptoms showed significant improvement from day 8 onward for patients switching for lack of efficacy and for those switching for other reasons. These data reflect observations in acute patients switched from oral antipsychotic agents in PALMFlexS (Hargarter/Schreiner et al: acute patients switched from oral antipsychotics [manuscript in preparation]) and the early treatment response seen in other studies with PP.[52,53]

Patient satisfaction with antipsychotic treatment is an important aspect in improving treatment continuation, as indicated in the SOHO (Schizophrenia Outpatient Health Outcomes)[54] and the CATIE (Clinical Antipsychotic Trial of Intervention Effectiveness) studies.[23] In the present study, patient satisfaction and completion rates were high, which support previous data that positive experiences with LAT can be associated with high patient acceptance and even preference.[55–57] Patient functioning and illness-related disabilities in activity and participation improved significantly during the study. With only 30% to 35% of patients with schizophrenia currently achieving remission[58,59] and 13.5% achieving recovery,[60] the improved functioning observed here in schizophrenia patients deemed stable suggests that further clinically relevant improvement of functioning and daily abilities is an important yet achievable outcome.

In the literature, data suggest that an improvement in a patient's subjective well-being is more predictive of enduring symptomatic remission to antipsychotic medication than psychotic symptoms in PANSS.[61,62] Research indicates that subjective well-being or quality of life is improved more by atypical antipsychotic agents than by conventional antipsychotic agents, they can also influence treatment adherence, and atypical agents improve the likelihood of patients achieving remission.[63,64] Collectively, these data strongly suggest that assessing a patient's perspective of antipsychotic treatment can exert clinical advantages because this perspective may be associated with increased adherence and thus improvements in long-term prognosis and outcomes.

AEs are a frequent reason why patients discontinue their antipsychotic medication.[23,65] In the present study, clinically relevant AEs such as EPMS, sedation, potentially prolactin-related TEAEs, and weight gain were low and consistent with randomized controlled studies with PP.[38,39] This finding suggests that PP is also generally well tolerated in a more diverse patient population with higher rates of comorbidities, comedications, and substance abuse. Notably, the percentage of patients with substance abuse in this study was lower than expected in routine clinical practice, which may reflect an investigator selection bias. However, the prevalence of current substance use in patients with schizophrenia, based on the CATIE study (which used the Structured Clinical Interview for DSM-IV Axis I Disorders) was 15.8%,[66] a rate which is similar to that reported in the present study, bearing in mind it did not use a structured interview for evaluating substance use disorder. Nevertheless, including patients with substance use disorder in clinical studies provides additional useful information for day-to-day practice.

The mean baseline BMI in this study (27.6 kg/m^2) was comparable to that reported in other large pragmatic studies, such as the SOHO study[67] and in a cohort of patients with chronic schizophrenia in Italy.[68] It was somewhat lower than that in a recent US trial[33,37] but considerably higher than that reported in the European First-Episode Schizophrenia Trial.[69] These varying findings highlight that there are substantial differences between newly diagnosed and patients with schizophrenia treated longer term, as

well as regional differences, that may influence antipsychotic choice or dosing. One additional, clinically interesting observation in the present study was the decline in the proportion of patients requiring concomitant use of a benzodiazepine or anticholinergic medication, suggesting that PP can be used effectively in monotherapy in a higher proportion of patients compared with previous oral antipsychotic treatment.

Study limitations include the unblinded treatment and the lack of an active comparator group. As such, these data do not provide a head-to-head comparison between treatments but suggest that suboptimal treatment with 1 antipsychotic medication does not predict failure with other antipsychotic agents, including PP. Because this study was unblinded and did not include a comparison group, reporting bias in the study results cannot be ruled out. Comparison between treatments was not the primary aim of this trial, which was designed to capture data in a setting mimicking daily clinical practice that is not normally achieved in randomized controlled trials. Nevertheless, the method used in this study is consistent with current standards used in clinical trials and therefore allows at least some indirect comparisons with data from interventional studies of a similar design. In addition, the present study did not exclude patients with current substance use or abuse, the exception being intravenous drug use; this is in contrast to the pivotal randomized controlled studies in PP that excluded patients if they had a DSM-IV diagnosis of active substance dependence within 3 months before screening.[37–39] There was little alcohol/substance use in this group of patients, and it cannot be ruled out that the psychiatrists selected patients who they felt would be most likely to complete the study.

CONCLUSIONS

These data illustrate that nonacute patients with schizophrenia considered stable by their physician show further clinically relevant symptom improvement and improvements in measures of functioning when switched from oral antipsychotic agents to PP.[36]

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Dr. Schreiner contributed to the literature search, study design, data analysis and interpretation, manuscript development and review. Dr. Rancans contributed to data collection and interpretation and manuscript review. Dr. Bez contributed to data collection and interpretation, manuscript development and review. Dr. Parellada contributed to data collection and interpretation. Dr. Carpiniello contributed to data collection and statistical analysis. Dr. Vidailhet contributed to data collection and interpretation and manuscript review. Mr. Bergmans contributed to

statistical analysis. Dr. Cherubin contributed to study management, data interpretation, manuscript development and review. Ms. Keim contributed to the operational management of the global clinical trial. Dr. Hargarter was the physician responsible for the study, the responsible medical officer of the sponsor and contributed to study design, study conduct, data analysis and interpretation, manuscript development and review.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

SUPPLEMENTAL MATERIAL

A supplemental table accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.08.014

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Supplemental Table. Secondary outcomes, Positive and Negative Syndrome Scale Marder factor scores. Values are given as mean (SD).

	Baseline Score	LOCF End Point	Change From Baseline to LOCF End Point
Positive symptoms factor score (SD)			
All patients (n = 589)	19.4 (5.6)	16.0 (6.0)	−3.3 (5.4)*
Patients switched for lack of efficacy (n = 143)	21.6 (4.8)	18.5 (6.1)	−3.1 (5.6)*
Patients switched for other reasons (n = 446)	18.7 (5.7)	15.3 (5.7)	−3.4 (5.4)*
Negative symptoms factor score			
All patients (n = 589)	19.6 (5.6)	16.1 (5.7)	−3.5 (5.3)*
Patients switched for lack of efficacy (n = 143)	22.4 (5.2)	18.6 (5.3)	−3.8 (4.9)*
Patients switched for other reasons (n = 446)	18.6 (5.4)	15.2 (5.6)	−3.4 (5.4)*
Disorganized thoughts factor score			
All patients (n = 589)	16.2 (4.4)	13.9 (4.6)	−2.3 (3.9)*
Patients switched for lack of efficacy (n = 143)	18.3 (3.7)	16.1 (4.1)	−2.2 (3.8)*
Patients switched for other reasons (n = 446)	15.5 (4.4)	13.2 (4.5)	−2.3 (4.0)*
Uncontrolled hostility/excitement factor score			
All patients (n = 589)	7.1 (2.6)	6.2 (2.7)	−0.9 (2.9)*
Patients switched for lack of efficacy (n = 143)	7.7 (2.5)	6.7 (2.8)	−1.0 (3.1)*
Patients switched for other reasons (n = 446)	6.9 (2.7)	6.0 (2.7)	−0.9 (2.8)*
Anxiety/depression factor score			
All patients (n = 589)	9.3 (3.1)	7.6 (3.1)	−1.7 (3.2)*
Patients switched for lack of efficacy (n = 143)	10.3 (3.2)	8.3 (3.5)	−2.0 (3.2)*
Patients switched for other reasons (n = 446)	9.0 (3.0)	7.3 (3.0)	−1.6 (3.2)*

LOCF = last-observation-carried-forward.
*$P < 0.0001$, Wilcoxon signed-rank test.