One-Year Open-Label Safety and Efficacy Study of Paliperidone Extended-Release Tablets in Patients With Schizophrenia

Michelle Kramer, MD, MPH, George Simpson, MD, Valentinas Maciulis, MD, PhD, Stuart Kushner, MD, Yanning Liu, MS, Pilar Lim, PhD, David Hough, MD, Joseph Palumbo, MD, and Mariëlle Eerdekens, MD, MBA

ABSTRACT

Introduction: This 52-week open-label extension (OLE) to a double-blind placebo-controlled recurrence prevention study examined the long-term safety and efficacy of flexibly-dosed paliperidone extended-release (ER) tablets in patients with schizophrenia.

Methods: Patients entering the OLE either entered from the double-blind phase (placebo or paliperidone ER treatment) or entered directly from the run-in or stabilization phase (paliperidone ER) of the earlier study. During the OLE, patients were treated with flexibly-dosed paliperidone ER (3–15 mg/day; 9 mg starting dose).

FOCUS POINTS
- Schizophrenia is a serious chronic mental condition requiring long-term effective management and intervention.
- Prevention of symptom recurrence is the principal aim in treating patients with schizophrenia.
- Paliperidone extended release (ER) has demonstrated efficacy and tolerability in delaying symptom recurrence in previous short-term randomized trials.
- Information on long-term safety of paliperidone ER in patients with schizophrenia is limited.
- This 1-year, open-label, extension study demonstrates the long-term safety and tolerability of paliperidone ER in patients with schizophrenia.

Safety and tolerability assessments included incidence of adverse events and extrapyramidal symptoms. Efficacy was also assessed.

Results: The study population (n=235) was predominantly men (66%), 18–58 years of age. Twelve patients (5%) experienced an adverse event requiring treatment discontinuation. One or more serious treatment-emergent adverse events were reported in 13 patients (6%). There was one death. The mean Positive and Negative Syndrome Scale total score decreased from open-label baseline to endpoint for all groups, regardless of previous double-blind treatment (placebo or paliperidone ER).

Conclusion: This year-long OLE provides information on the long-term safety and tolerability of paliperidone ER in patients with schizophrenia. The resulting safety and tolerability profile was similar to that seen in earlier short-term studies.

CNS Spectr. 2010;15(8):506-514.

INTRODUCTION

Schizophrenia is a chronic illness that requires long-term treatment in most cases.[1] Approximately 40% of schizophrenia patients are noncompliant with their medication regimen at any given time.[2] Different factors contributing to noncompliance have been noted, including but not limited to: poor symptom control,[3] dissatisfaction with adverse effects,[4] or patient belief that the medication was unnecessary.[5]

Paliperidone extended-release (PALI ER) is an oral antipsychotic approved for the acute and maintenance treatment of schizophrenia in the European Union, United States, and other countries. It provides consistent and continual drug delivery over a 24-hour period[6] and its unique pharmacokinetic profile reduces the need for initial dose titration. Because paliperidone undergoes limited hepatic metabolism, the potential for drug-drug interactions is reduced.

BACKGROUND

The recommended dose of PALI ER is 6 mg QD; doses from 3–15 mg have been studied. Previous 6-week randomized, double-blind studies demonstrated the efficacy and safety of PALI ER in the treatment of patients with acute schizophrenia.[7,8] The efficacy and safety of PALI ER for the prevention of symptom recurrence in patients previously stabilized on PALI ER was assessed in a double-blind placebo-controlled study.[9] We report here the safety and efficacy results of a 1-year open-label extension (OLE) to this double-blind symptom recurrence study. These data provide information on the long-term safety and efficacy of PALI ER. In addition, this study provided an opportunity to examine the effect of reinstating PALI ER treatment in patients who experienced interruption of active treatment as a result of their placebo assignment in the preceding double-blind trial.

METHODS

Patients

This institutional review-board approved study included consenting patients 18–65 years of age (inclusive) with a diagnosis of schizophrenia (based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria). All patients were capable of compliant, self-administration of medication or having assistance with medication. Patients who experienced a recurrence event during the double-blind phase remained recurrence free until the end of the double-blind phase of the study or were in the run-in (RI) or stabilization (ST) phases when the double-bind phase of the study was terminated were allowed to enter the OLE.

Patients were excluded from the double-blind study if they had a *DSM-IV* primary diagnosis other than schizophrenia, had history of current substance dependence, were at significant risk for suicidal or aggressive behavior, received any disallowed psychotropic medication within 3 days before the double-blind baseline of this study or received any injection of a depot antipsychotic since entering the double-blind phase, or had a documented complete lack of response to risperidone. Women were excluded if pregnant, nursing, or planning to become pregnant. Patients who discontinued study treatment during the double-blind phase for reasons other than recurrence were not eligible to enter the OLE phase.

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and was performed consistent with Good Clinical Practices and applicable regulatory requirements. All participants provided written informed consent.

Study Design

The study was conducted from September 2004 to August 2006 at 37 centers in India, Latvia, Lithuania, Romania, Turkey, and the US. The original study consisted of five phases: screening (up to 5 days); an 8-week RI phase during which eligible patients received open-label PALI ER (3–15 mg once daily; starting dose 9 mg), maintaining a stable dose for the final 2 weeks; a 6-week open-label ST phase during which patients remained on their previous dose; a double-blind treatment phase of variable duration during which stabilized patients were randomized to receive PALI ER (starting at the dose maintained during ST) or placebo; and this 52-week OLE (Figure 1). The double-blind recurrence prevention study was terminated at the interim analysis, as a result of positive efficacy for PALI ER versus placebo.

Patients who entered the OLE, therefore, had received previous treatment with PALI ER for varying lengths of time, determined by the phase of the previous study they were in at the time of its early termination. Patients who entered the OLE from the RI phase (8 weeks; flexibly-dosed PALI ER) or ST phase (6 weeks; PALI ER at the dose at which they had been stabilized in the RI phase) of the previous study formed the PALI ER (–double-blind [db])/PALI ER group (n=83). Patients who entered the OLE from the variable-duration double-blind phase had been randomized to receive placebo or PALI ER. Patients receiving placebo therefore had an interruption in treatment with PALI ER (ie, between the ST phase and OLE). They formed the placebo (PBO)/PALI ER group in the OLE (n=80). Patients who had been randomized to PALI ER in the double-blind phase formed the PALI ER (+double-blind [db])/PALI ER group (n=72) in the OLE.

During the OLE, study visits occurred weekly for the first 4 weeks and every 4 weeks thereafter until week 52. All patients entering the OLE received PALI ER 9 mg/day, which could be increased by 3 mg/day up to a maximum of 15 mg/day or decreased to a minimum of 3 mg/day as deemed necessary by the investigator. Oral benzodiazepines, oral benztropine, or biperiden (or equivalent agents) for the treatment of extrapyramidal symptom (EPS) control, and β-adrenergic blockers for treatment-emergent akathisia were allowed. Antidepressants (excluding monoamine oxidase inhibitors) were allowed if the dose was stable. Supportive or educational psychotherapy was also allowed. The results of the OLE phase are presented here.

Assessments

Safety was assessed by monitoring spontaneously reported treatment-emergent adverse events (TEAEs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), body weight and body mass index, and 12-lead electrocardiogram.

The efficacy assessments included changes from the OLE baseline to OLE endpoint in Positive and Negative Syndrome Scale (PANSS) total score,[10] the PANSS factor scores for positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility or excitement, and anxiety or depression,[11] Personal and Social Performance Scale scores, and Clinical Global Impression-Severity scores.

Analyses

Because the primary objective of this OLE study was to assess long-term safety and tolerability, no formal sample size calculation was

FIGURE 1.
Study design and patient disposition

	PBO/PALI ER (n=80) n (%)	PALI ER (+db) /PALI ER (n=72) n (%)	PALI ER (–db) /PALI ER (n=83) n (%)
Completed	50 (63)	48 (67)	44 (53)
Withdrawn			
Patient choice	13 (16)	15 (21)	22 (27)
Adverse event	9 (11)	1 (1)	4 (5)
Lack of efficacy	3 (4)	4 (6)	6 (7)
Lost to follow-up	4 (5)	2 (3)	3 (4)
Death	0	0	1 (1)
Other	1 (1)	2 (3)	3 (4)
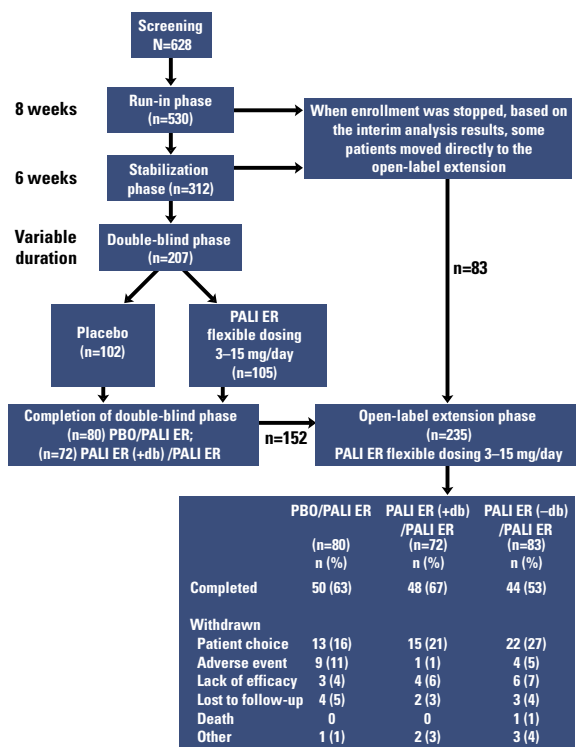
PALI ER=paliperidone extended-release; PBO=placebo; db=double-blind.
Kramer M, Simpson G, Maciulis V, et al. *CNS Spectr.* Vol 15, No 8. 2010.

performed. Time-to-discontinuation for any reason was summarized in a Kaplan-Meier plot.

The safety analysis set included all patients who received at least one dose of PALI ER; the intent-to-treat analysis set included all patients who took at least one dose of PALI ER and had one postbaseline efficacy assessment.

RESULTS

Patient Disposition

Of the 235 patients (safety analysis set) who entered the OLE phase, 60% (n=142) completed the 52-week study: 63% (n=50) in the PBO/PALI ER group; 67% (n=48) in the PALI ER (+db)/PALI ER group; and 53% (n=44) in the PALI ER (–db)/PALI ER group (Figure 1). The most common reason for discontinuation across treatment groups was patient choice 21% (n=50), although the specific reasons for discontinuation due to patient choice were not collected. The only available information in this regard is that 6 of the 50 patients (who discontinued by their own choice) had a higher PANSS scores at the time of withdrawal than was recorded at the previous visit. Also, three patients had TEAEs that started before the withdrawal, which persisted at the time of withdrawal. At all time points, the withdrawal rates from the OLE were highest for patients who participated only in the RI/ST phases compared with those who were randomized into the recurrence prevention period and received either double-blind placebo or double-blind PALI ER. Discontinuation occurred at a relatively constant rate throughout the OLE (Figure 2).

Demographic and Baseline Characteristics

The demographic and baseline characteristics were generally similar across groups (Table 1). The study population was predominantly men (66%) with a mean (SD) age of 36 (9.8) years (range: 18–58 years of age). Most patients were either white (48%) or "other" race (46%, mainly from sites in India). The majority (78%, n=184) were diagnosed with paranoid schizophrenia; 45% had been hospitalized at least twice (and 26% at least 4 times) before the study.

Treatment Exposure and Concomitant Medications

The mean (SD) mode daily doses of PALI ER were similar across groups: 10.8 (3.15) mg/day (PBO/PALI ER), 10.8 (3.13) mg/day (PALI ER (+db)/PALI ER), and 11.9 (3.21) mg/day (PALI ER (–db)/PALI ER). The median duration of exposure to PALI ER during the OLE phase was also similar (362–364 days) across groups. Total exposure to PALI ER (from run-in baseline of the previous study to OLE endpoint) varied, however, and was shortest in the PALI ER (–db)/PALI ER group (median: 395 days) compared with the PBO/PALI ER (461 days) and PALI ER (+db)/PALI ER (481 days) groups. The median (range) duration of patient exposure to PALI ER before entering the OLE was 98.0 (96; 119) days for the PBO/PALI ER group, 140.5 (104; 428) days for the PALI ER (+db)/PALI ER group, and 78.0 (7; 102) days for the PALI ER (–db)/PALI ER group.

A total of 55 patients (23%) received benzodiazepines as rescue medication, with greater usage in the PALI ER (–db)/PALI ER group (n=23, 28%), than in the PBO/PALI ER (n=16; 20%) or PALI ER (+db)/PALI ER (n=16; 22%) groups. A total of 19 patients (8%) were treated with antidepressants: PBO/PALI ER (n=7; 9%), PALI ER (+db)/PALI ER (n=5; 7%), and PALI ER (–db)/PALI ER (n=7; 8%). Concomitant medications, other than oral benzodiazepines or antidepressants, were taken by 62% of all patients, with greater usage by patients who participated only in the RI/ST phase compared with those who entered the double-blind phase.

Safety

Overall, 69% (n=163/235) of patients experienced a TEAE with a higher incidence for patients in the PALI ER (–db)/PALI ER group (82%) com-

FIGURE 2.
Kaplan Meier plot of time to discontinuation for any reason
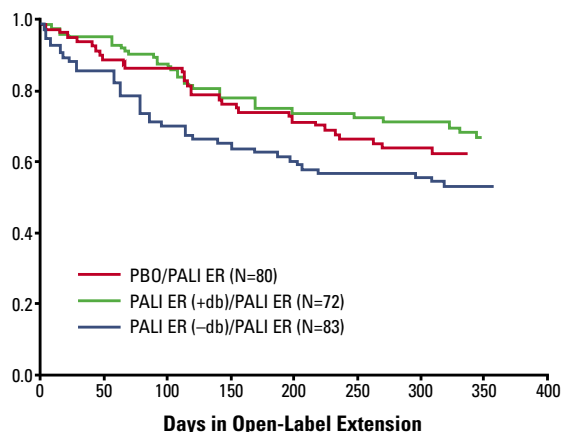
PBO=placebo; PALI ER=paliperidone extended-release; db=double-blind.

Kramer M, Simpson G, Maciulis V, et al. *CNS Spectr.* Vol 15, No 8. 2010.

pared with the other two groups (63% each) (Table 2). Serious TEAEs occurred in 6% (n=13) of patients overall: exacerbated schizophrenia was the most common of these (n=7; 3%), which includes adverse events (n=3 TEAEs) of exacerbated schizophrenia that began in the double-blind phase. One death (with bronchospasm and pulmonary thromboembolism considered in the differential diagnosis) was reported and was considered probably related to the study medication. Syncope as a serious TEAE was reported in one patient and considered possibly related to study drug. The TEAEs leading to study discontinuation occurred in 12 patients (5%): dyskinesia and depression occurred in 2 patients each, and the other TEAEs occurred in 1 patient each.

TABLE 1.

Demographic and Baseline (Run-in) Characteristics (Safety Analysis Set)

	PBO/PALI ER	PALI ER(+db) /PALI ER	PALI ER(–db) /PALI ER	Total
Demographics				
Age (years)				
Category, n (%)				
18–25	11 (14)	11 (15)	18 (22)	40 (17)
26–50	63 (79)	50 (69)	62 (75)	175 (74)
51–65	6 (8)	11 (15)	3 (4)	20 (9)
Mean (SD)	36.5 (9.83)	37.7 (10.07)	33.3 (9.22)	35.8 (9.83)
Sex, n (%)				
Men	50 (63)	41 (57)	63 (76)	154 (66)
Women	30 (38)	31 (43)	20 (24)	81 (34)
Race, n (%)				
White	4 (58)	41 (57)	25 (30)	112 (48)
Black	5 (6)	2 (3)	4 (5)	11 (5)
Asian	0	2 (3)	1 (1)	3 (1)
Other	29 (36)	27 (38)	53 (64)	109 (46)
Weight (kg)*				
Mean (SD)	73.9 (24.25)	69.3 (16.04)	62.4 (17.16)	68.4 (20.08)
Body mass index (kg/m²)†				
Category, n (%)				
Normal <25	42 (53)	39 (54)	59 (72)	140 (60)
Overweight 25–<30	20 (25)	26 (36)	13 (16)	59 (25)
Obese ≥30	18 (23)	7 (10)	10 (12)	35 (15)
Mean (SD)	26.0 (7.78)	24.6 (4.84)	22.7 (5.28)	24.4 (6.26)
Psychiatric History				
Age at diagnosis of schizophrenia (years)				
Mean (SD)	24.9 (7.95)	26.7 (8.79)	25.3 (8.19)	25.6 (8.30)
Baseline total PANSS				
Mean (SD)	93.7 (10.66)	93.0 (10.99)	89.3 (11.27)	91.9 (11.11)
Baseline CGI-S, n (%)				
Mild	0	1 (1)	2 (2)	3 (1)
Moderate	31 (39)	33 (46)	42 (51)	106 (45)
Marked	41 (51)	31 (43)	30 (36)	102 (43)
Severe	8 (10)	7 (10)	9 (11)	24 (10)

* Observed case: measured at baseline and endpoint.

† N=82 for PALI ER (–db)/PALI ER.

PBO=placebo; PALI ER=paliperidone extended-release; db=double-blind; SD=standard deviation; PANSS=Positive and Negative Syndrome Scale; CGI-S=Clinical Global Impression-Severity.

Kramer M, Simpson G, Maciulis V, et al. *CNS Spectr.* Vol 15, No 8. 2010.

There were no reports of neuroleptic malignant syndrome or anaphylactic reaction. Three TEAEs related to suicidality were reported: one was a suicide attempt, considered serious, resulted in study discontinuation and two reports of suicidal ideation, which resulted in permanent discontinuation of medication in one patient and temporary discontinuation of medication in the other.

Tremor (13%, n=31) and akathisia (11%, n=25) were the most frequently reported EPS-related TEAEs (Table 2), and were highest in the PALI ER (–db)/PALI ER group (tremor: 19%, n=16; akathi-sia: 17%, n= 14). None was reported to be serious. At baseline, treatment for EPS-related symptoms was prescribed for 33% of patients in the PALI ER (–db)/PALI ER group, compared with 19% in the PBO/PALI ER and 25% in the PALI ER (+db)/ PALI ER groups. The use of these medications increased across groups during the trial: Anti-EPS or antihistamine medication was required by 49% of patients in the PALI ER (–db)/PALI ER group, 30% in the PBO/PALI ER and 31% in the PALI ER (+db)/PALI ER groups in the OLE phase.

TABLE 2.
Treatment-Emergent Adverse Events* (Safety Analysis Set)

	PBO/PALI ER (n=80) n (%)	PALI ER(+db)/PALI ER (n=72) n (%)	PALI ER(–db)/PALI ER (n=83) n (%)
Overall TEAEs	50 (63)	45 (63)	68 (82)
Possibly drug-related TEAEs	33 (41)	29 (40)	41 (49)
One or more serious TEAEs	5 (6)	4 (6)	4 (5)
TEAEs leading to discontinuation	8 (10)	1 (1)	3 (4)
TEAEs in at least 5% of patients in any group			
Total no. patients with adverse events	50 (63)	45 (63)	68 (82)
Akathisia	7 (9)	4 (6)	14 (17)
Tremor	6 (8)	9 (13)	16 (19)
Headache	5 (6)	5 (7)	9 (11)
Pyrexia	5 (6)	3 (4)	7 (8)
Amenorrhea	5 (6)	4 (6)	3 (4)
Insomnia	4 (5)	3 (4)	11(13)
Dizziness	4 (5)	1 (1)	8 (10)
Schizophrenia	4 (5)	4 (6)	5 (6)
Dyskinesia	4 (5)	3 (4)	1 (1)
Cough	4 (5)	0	0
Anxiety	3 (4)	8 (11)	5 (6)
Depression	3 (4)	1 (1)	4 (5)
Weight increase	2 (3)	2 (3)	5 (6)
Somnolence	2 (3)	0	4 (5)
Nasopharyngitis	2 (3)	0	4 (5)
Drooling	1 (1)	2 (3)	7 (8)
Salivary hypersecretion	1 (1)	2 (3)	6 (7)
Parkinsonian gait	1 (1)	3 (4)	6 (7)
Cogwheel rigidity	1 (1)	4 (6)	9 (11)

* TEAEs are those that were spontaneously reported by patients. Patients entered this open-label extension from a previous double-blind study, where they were receiving either placebo treatment, flexibly-dosed paliperidone ER, or were still in the Run-in/Stabilization phase.

PBO=placebo; PALI ER=paliperidone extended-release; db=double-blind; TEAEs=treatment-emergent adverse events; no.=number.

Kramer M, Simpson G, Maciulis V, et al. *CNS Spectr.* Vol 15, No 8. 2010.

Overall, 37% required anti-EPS medication or antihistamines during the OLE compared with 26% at baseline.

Somnolence was reported in 3% (n=6) and sedation in 2% (n=5) of patients across treatment groups. Tachycardia and sinus tachycardia were reported in 2% (n=5) of patients each across treatment groups with the highest incidence (1%, n=3) for each event in the PALI ER (–db)/PALI ER group.

At OLE baseline, the median prolactin levels were: 8.18 ng/mL (men), 15.15 ng/mL (women) in PBO/PALI ER group; 43.81 ng/mL (men), 133.54 ng/mL (women) in PALI ER (+db)/PALI ER group; 43.72 ng/mL (men), 148.22 ng/mL (women) in PALI ER (–db)/PALI ER group. As shown by the change from OLE baseline to endpoint values, median prolactin levels increased during the OLE in the PBO/PALI ER group (men: 26.79 ng/mL, women: 102.75 ng/mL) and remained relatively stable or decreased in both the PALI ER (+db)/ PALI ER (men: -3.28 ng/mL, women: -3.00 ng/mL) and PALI ER (–db)/PALI ER groups (men: -3.43 ng/ mL; women: -59.97 ng/mL). Amenorrhea (n=12) and irregular menstruation (n=1) were the potentially prolactin-related TEAEs reported and led to discontinuation in one patient (amenorrhea).

No reports of glucose-related TEAEs or treatment-emergent markedly elevated glucose values were observed. Orthostatic hypotension was reported in one patient. There was one report of oculogyration of mild severity and none of tardive dyskinesia as assessed by changes in AIMS scores and TEAEs. A modest increase in mean weight gain (1.5 kg) was observed across the three treatment groups. Weight increase of ≥7% occurred in 19 % (n=37) of patients overall, with the lowest incidence (11 %, n=7) in the PALI ER (+db)/PALI ER group. No patient had a QTc interval value ≥500 ms during any of the study phases. There were no noteworthy changes for most of the laboratory analytes, including mean liver function, renal function, serum lipids and serum glucose values. There were no clinically relevant mean changes in vital signs.

Efficacy

Patients entering the OLE had demonstrated significant decreases (improvement) in mean PANSS total scores following treatment with PALI ER in the RI/ST phase and during the double-blind phase of the earlier study (ie, for those patients so randomized). At OLE baseline, the mean (SD) PANSS scores were high in the PBO/PALI ER group (68.5 [22.90]) compared with the PALI ER (+db)/PALI ER (54.5 [17.81]) and PALI ER (–db)/PALI ER groups (54.3 [15.09]). Patients who entered the OLE from the placebo group had not taken active medication for a median of 36.5 days and thus had higher PANSS scores at OLE baseline compared with the other treatment groups who were receiving PALI ER at OLE baseline (Figure 3).

Subsequently, the PBO/PALI ER group improved the most during treatment with PALI ER in the OLE (Table 3). Notably, patient groups who had received PALI ER in the earlier study (median duration of 45 days) showed additional improvement from OLE baseline to endpoint in PANSS total scores. Changes in other efficacy measures were generally consistent with these trends seen in the PANSS total scores and suggested improvement from OLE baseline to endpoint irrespective of previous treatment, with the most improvement demonstrated in the PBO/PALI ER group.

DISCUSSION

Most patients treated for schizophrenia do not continue over the long term with the first medication they are prescribed.[2] The reasons for changing treatments are varied, but among them are poor symptom control and poor tolerability. The effective medication for a particular patient is the one with the most acceptable combination of

FIGURE 3.

Changes in PANSS total score: double-blind versus open-label treatment (intent-to-treat analysis set)
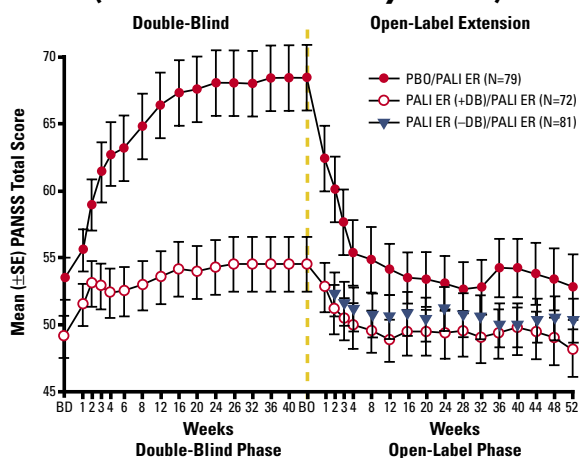
PANSS=Positive and Negative Syndrome Scale; SE=standard error; BD=baseline double-blind; BO=baseline open-label; PBO=placebo; PALI ER=paliperidone extended-release; DB=double-blind.

Kramer M, Simpson G, Maciulis V, et al. *CNS Spectr*. Vol 15, No 8. 2010.

efficacy and tolerability, as judged by physician and patient. Sixty percent of the 235 patients who entered this year-long extension study completed the study. This is consistent with completion rates in other long -term studies in this indication.[12] Most of the patients in this study discontinued by their own choice, with no further information available on the reasons these patients withdrew.

The safety profile of flexibly-dosed (3–15 mg, once daily) PALI ER in this 52-week OLE was consistent with the results of the previous double-blind phase as well as those from previous 6-week short-term studies of PALI ER.[78] No new safety concerns emerged. Patients who entered the OLE directly from the RI/ST phases of the previous double-blind study (and who therefore had the shortest previous exposure to PALI ER when they entered) reported a higher incidence of TEAEs, although this did not result in higher discontinuations. Our results suggest that the overall incidence of TEAEs decreases with continued use of PALI ER.

At all time points, the withdrawal rates from the OLE were highest for patients who participated only in the RI/ST phases compared with those who received either double-blind placebo or double-blind PALI ER treatment. Patient choice was most frequently cited as the reason for withdrawal. This may be associated with inadequate symptom relief during the establishment of a patient's effective dose, which is supported by the greater use of concomitant medications by patients in the PALI ER (–db)/PALI ER group. The TEAEs, although more frequently reported by patients from the PALI ER (–db)/PALI ER group compared with other groups, did not appear to frequently result in withdrawal for this group.

Consistent with the known pharmacology of PALI ER, median prolactin levels remained above normal at OLE endpoint in all treatment groups. The PBO/PALI ER group, which had an interruption in PALI ER treatment of more than 1 month during the double-blind phase and was reintroduced to PALI ER during the OLE phase, experienced the greatest elevation in the median prolactin levels. The median prolactin levels for the other two treatment groups who continued on PALI ER treatment from the earlier study, remained relatively stable during the OLE phase. None of the potentially prolactin-related TEAEs were reported as serious, although spontaneous reporting can result in underreporting of actual incidences of sexual dysfunction.

Of the number of EPS-related TEAEs during the study, the incidences of akathisia and tremor were most frequent. Consistent with this, the use of anti-EPS medication or antihistamines increased during the OLE from baseline.

All treatment groups showed additional improvement in efficacy measures from OLE baseline. Not surprisingly, the PBO/PALI ER group, which had comparatively worsened scores at OLE baseline, improved the most in all measures. Notably, patients who received uninterrupted treatment with PALI ER showed additional improvement from their baseline scores during the OLE across efficacy measures. These findings support the importance of continuous treatment for schizophrenia in order to maximize improvements.[13]

TABLE 3.
Efficacy Assessments (Intent-To-Treat Analysis Set)

Change from OLE Baseline to OLE Endpoint	PBO/PALI ER (n=79)	PALI ER (+db)/PALI ER (n=72)	PALI ER (–db)/PALI ER (n=81)
Mean (SD) PANSS total score	-15.7 (20.09)	-6.3 (18.91)	-3.9 (13.85)
PANSS Factor Scores, Mean (SD)			
Positive symptoms	-5.0 (5.96)	-2.0 (6.61)	-1.7 (5.01)
Negative symptoms	-2.5 (6.00)	-1.5 (5.22)	-0.9 (3.86)
Disorganized thoughts	-3.4 (4.58)	-1.6 (3.91)	-0.9 (3.06)
Uncontrolled hostility/excitement	-2.7 (3.79)	-0.5 (3.69)	-0.1 (2.33)
Anxiety/depression	-2.1 (3.37)	-0.7 (3.42)	-0.3 (2.63)
Clinical Global Impression Severity Scale Median (Range)	-1.0 (-4;2)	0.0 (-3;3)	0.0 (-2;2)
Personal and Social Performance Scale	12.7(15.18)	6.6(15.28)	4.8(14.28)

OLE=open-label extension; PBO=placebo; PALI ER=paliperidone extended-release; db=double-blind; SD=standard deviation; PANSS=Positive and Negative Syndrome Scale.

Kramer M, Simpson G, Maciulis V, et al. *CNS Spectr.* Vol 15, No 8. 2010.

This study used a 9 mg/day starting dose for PALI ER. Subsequent research[78] showed that doses of 3 and 6 mg/day were also efficacious and 6 mg/day is the best starting dose. Thus, patients in this study may have received higher doses in some cases than might have been necessary. As the study enrolled a predominately white population, the degree to which these results may apply to more racially diverse populations is not known. An additional study limitation is that there was no control group. However, given the demonstrated benefit of PALI ER during the earlier double-blind phase,[9] continued therapy with placebo was considered inappropriate.

CONCLUSION

This year-long OLE expands the safety and tolerability data for PALI ER and demonstrates a safety and tolerability profile that is consistent with results from previous placebo-controlled studies, including the recurrence prevention study that immediately preceded this study.[9] Additionally, it appears that the best symptom relief is obtained when treatment is continued without interruption. ***CNS***

REFERENCES

1. Mancevski B, Keilp J, Kurzon M, et al. Lifelong course of positive and negative symptoms in chronically institutionalized patients with schizophrenia. *Psychopathology.* 2007;40(2):83-92.
2. Valenstein M, Ganoczy D, McCarthy JF, Myra Kim H, Lee TA, Blow FC. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. *J Clin Psychiatry.* 2006;67(10):1542-1550.
3. Liu-Seifert H, Adams DH, Kinon BJ. Discontinuation of treatment of schizophrenic patients is driven by poor symptom response: a pooled post-hoc analysis of four atypical antipsychotic drugs. *BMC Med.* 2005; 3:21.
4. Yamada K, Watanabe K, Nemoto N, et al. Prediction of medication noncompliance in outpatients with schizophrenia: 2-year follow-up study. *Psychiatry Res.* 2006;141(1):61-69.
5. Cooper C, Bebbington P, King M, et al. Why people do not take their psychotropic drugs as prescribed: results of the 2000 National Psychiatric Morbidity Survey. *Acta Psychiatr Scand.* 2007;116(1):47-53.
6. Karlsson P, Dencker E, Nyberg S, et al. Pharmacokinetics, dopamine D_2 and serotonin 5-HT$_{2A}$ receptor occupancy and safety profile of paliperidone extended-release in healthy subjects. *Schizophr Res.* 2006;81(Suppl 1):85-86.
7. Kane J, Canas F, Kramer M, et al. Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. *Schizophr Res.* 2007;90(1-3):147-161.
8. Davidson M, Emsley R, Kramer M, et al. Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): Results of a 6-week, randomized, placebo-controlled study. *Schizophr Res.* 2007;93(1-3):117-130.
9. Kramer M, Simpson G, Maciulis V, et al. Paliperidone extended release tablets for prevention of symptom recurrence in patients with schizophrenia: A randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol.* 2007;27(1):6-14.
10. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261-276.
11. 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(12):538-546.
12. Kane JM, Lauriello J, Laska E, et al. Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol.* 2008;28(2 Suppl 1):S29-S35.
13. Kane JM. Pharmacologic treatment of schizophrenia. *Biol Psychiatry.* 1999;46(10):1396-1408.

514