A Randomized, Double-Blind, Placebo-Controlled Study of 2 Dose Ranges of Paliperidone Extended-Release in the Treatment of Subjects With Schizoaffective Disorder

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Objective: This study was designed to assess efficacy and safety of paliperidone extended-release (ER) in patients with schizoaffective disorder.

Method: A randomized, 6-week, double-blind, placebo-controlled study was conducted. Subjects with a Structured Clinical Interview for *DSM-IV* diagnosis of schizoaffective disorder, Positive and Negative Syndrome Scale (PANSS) total score ≥ 60, score ≥ 4 on ≥ 2 PANSS items (hostility, excitement, tension, uncooperativeness, poor impulse control), and Young Mania Rating Scale and/or Hamilton Depression Rating Scale, 21-item version scores ≥ 16 were eligible. Subjects received higher-dose (12 mg/d) or lower-dose (6 mg/d) paliperidone ER. Dose adjustments by 3-mg increments were allowed until day 15. The study was conducted from October 2006 through February 2008.

Results: A total of 316 subjects were randomly assigned to paliperidone ER lower dose (n = 109), higher dose (n = 100), or placebo (n = 107). Mean ± SD modal dose in lower- and higher-dose groups: 5.7 ± 0.9 and 11.6 ± 1.0 mg/d, respectively. Mean ± SE PANSS total score (primary outcome) improved significantly with higher-dose paliperidone ER versus placebo (–32.4 ± 2.1 versus –24.1 ± 2.1; $P = .003$). Change with lower-dose paliperidone ER (–27.7 ± 2.1) was not significantly different from placebo ($P = .187$). No new safety issues were identified; common adverse events were headache (placebo: 16.8%; paliperidone ER: lower dose, 13.9%, higher dose, 13.3%) and tremor (3.7%, 12.0%, 11.2%, respectively). Mean prolactin and weight changes were greater with active treatment than placebo.

Conclusions: Higher-dose paliperidone ER was effective and well tolerated in patients with acute schizoaffective disorder. These findings and those from a companion study constitute the first registration program for antipsychotic treatment in schizoaffective disorder.

Trial Registration: clincaltrials.gov Identifier: NCT00397033

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Schizoaffective disorder is a chronic and disabling mental illness, characterized by the concurrent presentation of symptoms of schizophrenia and prominent affective symptoms consistent with a major mood episode. The coexistence of these symptoms results in an illness course that is distinct from those of schizophrenia and affective disorders.

According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*), schizoaffective disorder is characterized by an uninterrupted period of illness during which there is a major depressive, manic, or mixed episode concurrent with criterion A for schizophrenia (2 or more of the following symptoms: hallucinations, delusions, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms). During that same period, psychotic symptoms must be present for at least 2 weeks in the absence of prominent mood symptoms, yet mood episodes must be present for a substantial portion of the total duration of the illness. *DSM-IV* further classifies schizoaffective disorder into bipolar and depressive types.

A careful longitudinal history often is required to assess the relationship of psychotic and affective symptoms and to determine which affective symptoms are present. Because of clinical differences in disease course characteristics, it is important to distinguish schizoaffective disorder from schizophrenia and from bipolar or major depressive disorders with psychotic features. A recent systematic literature review[1] of clinical trials that compared schizoaffective disorders with schizophrenia and/or mood disorders found that patients with schizoaffective disorder have the highest rate of hospitalizations and a higher rate of comorbid substance abuse than patients with schizophrenia. Further, patients with schizoaffective disorder appear to be at greater risk for suicidal behavior than patients with schizophrenia and mood disorders.[1,2]

The lifetime prevalence of schizoaffective disorder has been estimated at between 0.5% and 0.8%.[3] Although schizoaffective disorder occurs less commonly than schizophrenia,[4] it may account for up to one-quarter of admissions to inpatient mental health facilities.[5] Despite the frequent occurrence of schizoaffective disorder among the seriously mentally ill, little is known about how to manage this condition. Treatment is symptom driven, and patients are often maintained on complex therapeutic regimens as clinicians attempt to manage both the psychotic and affective symptoms.[6] Although antipsychotics are the cornerstone of treatment, they are commonly prescribed in combination with mood stabilizers and/or antidepressants.[7] Until recently, no medications were approved for schizoaffective disorder in the United States, and none are approved in the European Union and most other countries. Furthermore, no treatments have been systematically studied specifically in this patient population, nor are there treatment guidelines. Hence, there is a need for large, well-controlled trials with antipsychotics in this patient population.

In previous controlled studies, paliperidone extended-release (ER) demonstrated efficacy and a favorable safety profile in both patients with schizophrenia[8–11] and those with acute bipolar disorder with manic/mixed episodes.[12] Additionally, in a post hoc analysis[13] of 193 patients with schizophrenia and prominent affective symptoms, paliperidone ER provided significant improvements in Positive and Negative Syndrome Scale (PANSS)[14] total and all factor scores compared with placebo.

The present trial was part of a larger clinical program developed to support the first licensed indication for schizoaffective disorder. The primary objective of this study was to evaluate the efficacy and safety of 2 dose groups of paliperidone ER versus placebo in the treatment of schizoaffective disorder. Results of another trial from this program will be reported separately.[15]

METHOD

This randomized, double-blind, placebo-controlled, parallel-group study (study CR010498) was conducted at 44 centers in India, Russia, Ukraine, and the United States. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The protocol was approved by an institutional review board or an independent ethics committee at each center. All patients gave informed consent after the study procedures had been fully explained. The study was conducted from October 2006 through February 2008.

Subjects

Eligible subjects were inpatients (18 to 65 years old) with an acute exacerbation who met criteria for schizoaffective disorder as confirmed by the Structured Clinical Interview for *DSM-IV* disorders (SCID)[16] at screening. Subjects were required to have a PANSS total score of at least 60 and a score ≥ 4 on at least 2 of the following PANSS items: hostility (P7), excitement (P4), tension (G4), uncooperativeness (G8), and poor impulse control (G14). In addition, subjects needed to have prominent mood symptoms, with a score ≥ 16 on the Young Mania Rating Scale (YMRS)[17] and/or on the Hamilton Depression Rating Scale, 21-item version (HDRS-21).[18]

Exclusion criteria included first-episode psychosis, a diagnosis of major depressive disorder, bipolar disorder, schizophrenia or schizophreniform disorder, or any other Axis I diagnosis except substance abuse. Subjects with substance dependence diagnosed within the previous 6 months were also excluded, as were patients who had attempted suicide within the prior 12 months or were considered at significant risk for suicide. Subjects were permitted to enter if they were receiving treatment with antidepressants (with the exception of monoamine oxidase inhibitors) and/or mood stabilizers (with the exception of carbamazepine), provided that they were on a stable dose within 30 days of screening.

Design

The study included a screening period, followed by randomization and double-blind treatment for 6 weeks. During screening, subjects entered a washout period of 2 to 5 days, during which all other antipsychotic medications were discontinued. After the screening visit, all enrolled subjects remained hospitalized until at least the day 8 visit, after which they could be discharged if, based on the investigator's judgment, they were considered appropriate for outpatient care.

Randomization was stratified by site and by treatment with concomitant medications (mood stabilizers and/or antidepressants) versus no concomitant medications. Subjects were randomly assigned (1:1:1) to receive lower-dose paliperidone ER (6 mg/d, option to reduce to 3 mg/d), higher-dose paliperidone ER (12 mg/d, option to reduce to 9 mg/d), or placebo. If clinicians reduced a subject's dose, they had the option to return to the originally assigned dose within the first 15 days, but no dosage adjustments were permitted thereafter. Subjects receiving a benzodiazepine on a stable dose for at least 3 months before the study could continue that regimen during the study. For severe restlessness or agitation during the study, oral lorazepam could be used up to 4 mg/d until day 5 and up to 2 mg/d until day 15. To manage treatment-emergent movement disorders, benztropine (or its equivalent) could be initiated, at the discretion of the investigator, up to a maximum dosage of 4 mg/d. Subjects who discontinued study medication but had not withdrawn consent were required to complete all end-of-treatment (scheduled for final visit) assessments at discontinuation and were thereafter treated according to usual clinical practice. These subjects were asked to have the same assessments performed at the scheduled end-of-study (day 43) visit, unless consent was withdrawn.

Assessments

Efficacy was assessed by the PANSS, the Clinical Global Impressions-Severity of Illness Scale for Schizoaffective Disorder (CGI-S-SCA) and -Change Scale for Schizoaffective Disorder (CGI-C-SCA),[19] YMRS, and HDRS-21—each of which was performed at baseline, day 4, and weeks 1, 2, 3, 4, and 6. Investigators and raters were to have clinical and/or research experience with this population and to have participated in study-specific training, including training on the SCID. Raters were also required to score within ± 1 point of an expert-recommended score on 80% of the 30 PANSS items on the PANSS certification video. Whenever possible, efforts were made to use the same raters at each site to assess the same subjects throughout the study. The CGI-S-SCA is a syndrome-specific, 7-point scale that includes an overall severity score as well as 7-point scores for the positive, negative, manic, and depressive domains of the illness. It was specifically developed for this clinical trial program and is currently undergoing validation. A CGI-S-SCA rating of 1 is equivalent to "normal, not ill at all," and a rating of 7 is equivalent to "extremely ill patients." Likewise, the CGI-C-SCA is scored similarly to the original CGI-C but also measures change in the aforementioned 4 domains in addition to overall change.

The primary efficacy endpoint was the change in the PANSS total score from baseline to week 6 end point (last observation carried forward [LOCF]). Secondary efficacy endpoints included change from baseline to week 6 LOCF end point for the 5 PANSS factor scores, CGI-S-SCA scores, CGI-C-SCA scores, composite response (defined as the percentage of patients experiencing ≥ 30% improvement from baseline in PANSS total score and having a CGI-C-SCA score ≤ 2), time to first response to treatment, YMRS scores, and HDRS-21 scores.

Safety assessments included the reporting of adverse events at every treatment visit as well as clinical laboratory tests (including measurement of prolactin levels), vital signs, and physical examination (including body weight) at baseline and week 6. Movement disorders were assessed using the report of adverse events and the following scales: Simpson-Angus Scale (SAS),[20] Abnormal Involuntary Movement Scale (AIMS),[21] and Barnes Akathisia Scale (BAS)[22] evaluated at baseline and week 6. The InterSePT Scale for Suicidal Thinking (ISST)[23] was administered at baseline, day 8 or day of hospital discharge, and week 6 (or early withdrawal). An electrocardiogram (ECG) was recorded at screening, at baseline, and at the end-of-study visit.

Statistical Analysis

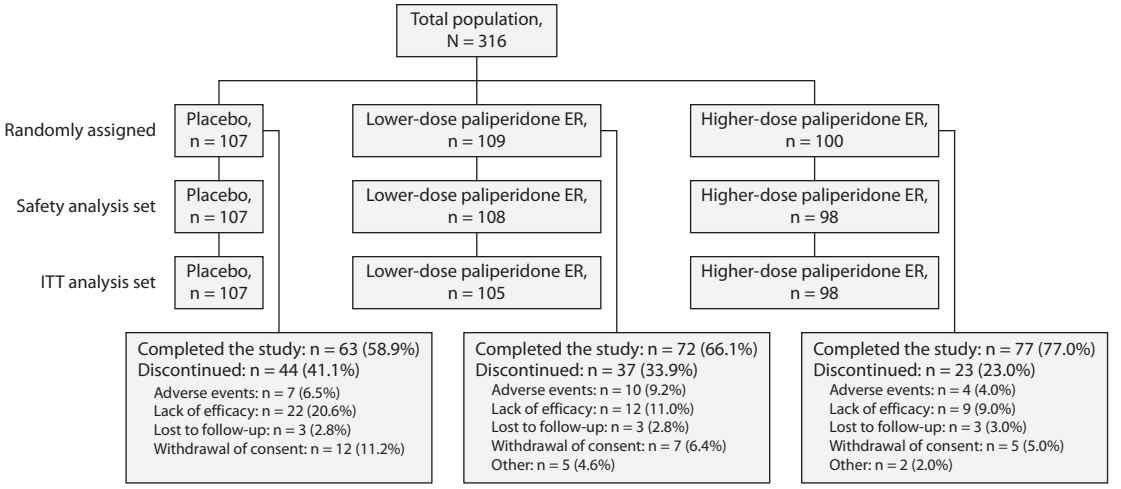
Study sample size was based on an assumption of a treatment difference of at least 11 points in change from baseline in PANSS total score between either paliperidone ER dose group and placebo, with an assumed standard deviation (SD) of 21.5 points. A .025 level of statistical significance was used to ensure that the less significant comparison would be significant with 90% power following the application of the Hochberg approach. Adjusting for a rate of 8% for subjects who would not have baseline or postbaseline efficacy assessments, the required number of subjects for each group was estimated to be 105—corresponding to a total sample size of 315 subjects.

The intent-to-treat (ITT) analysis set used for all efficacy analyses consisted of randomly assigned subjects who received at least 1 dose of study medication and had both baseline and at least 1 postbaseline PANSS assessments. Safety was analyzed for study subjects who received at least 1 dose of study medication. Baseline characteristics and safety assessments were summarized using descriptive statistics.

The 2 primary efficacy null hypotheses were that there was no difference in mean change from baseline to the week 6 LOCF end point in the PANSS total score (1) between the lower-dose paliperidone ER group and the placebo group and (2) between the higher-dose paliperidone ER group and the placebo group. The treatment group differences were evaluated using an analysis-of-covariance (ANCOVA) model. This model included treatment, concomitant medication stratum, and country as fixed-effect design factors and baseline PANSS total score as a covariate. The 2 primary pairwise comparisons were the paliperidone ER lower-dose group versus the placebo group and the paliperidone ER higher-dose group versus the placebo group, and the Hochberg step-up procedure was used to address multiplicity. Two-sided 95% confidence intervals (CIs) were computed for the difference in least squares (LS) mean change of each paliperidone ER group compared with placebo. Effect size (versus placebo) based on the LS means was also computed for the paliperidone ER groups. To address limitations of the LOCF approach, changes in PANSS total score at week 6 were also examined using a repeated-measures ANCOVA model. This model included the baseline score as a fixed-effect covariate; treatment, country, concomitant medication stratum, and time as fixed-effect factors; and the treatment-by-time interaction. The correlation of the repeated measurements for each subject was modeled using an unstructured covariance matrix. Missing data patterns were also examined. Within-group differences were evaluated using paired *t* tests. Treatment-by-concomitant medication stratum, treatment-by-region (US, non-US), and treatment-by-country interactions were explored using the same ANCOVA model as that for the analysis of primary endpoint with each interaction term included separately. Furthermore, for the primary efficacy endpoint, possible outliers were examined using Mahalanobis distances for each observation and compared with a critical value obtained from the χ^2 distribution at the .025 significance level. Treatment group differences were analyzed excluding these outliers using the same ANCOVA model as specified for the LOCF analysis of the PANSS total score.

Actual values and changes from baseline for numeric scores for the following secondary and other efficacy

Figure 1. Patient Disposition



Abbreviations: ER = extended-release, ITT = intent to treat.

variables were summarized at week 6 LOCF end point: PANSS factor scores, CGI-S-SCA, CGI-C-SCA (actual values only), HDRS-21 total score, and YMRS total score. The treatment group differences were analyzed based on the same ANCOVA model described for the primary efficacy analysis, except that the respective baseline score was used as the covariate. Secondary measures were also examined using a repeated-measures ANCOVA model. The CGI-C score was analyzed using an ANOVA model. Frequency counts and percentages of subjects reporting each CGI-S-SCA and CGI-C-SCA level were summarized. Treatment group differences for categorical outcomes including composite response were evaluated using the Cochran-Mantel-Haenszel test controlling for concomitant medication stratum and country. The distribution of time to first response was calculated using Kaplan-Meier estimates and compared among treatment groups using log rank test. All statistical tests for secondary analyses were 2-sided and conducted at the 5% significance level; no adjustments for multiplicity were performed.

RESULTS

Disposition, Baseline Demographics, and Clinical Characteristics

Of the 316 subjects who were screened and randomly assigned, 310 were included in the ITT group (placebo [n = 107], paliperidone ER higher-dose group [n = 98], and paliperidone ER lower-dose group [n = 105]) (Figure 1). Overall demographic and baseline characteristics of the ITT population were similar across all study groups (Table 1) except for a significant difference ($P < .05$) in PANSS total score between the placebo and paliperidone ER lower-dose groups. Most subjects (69.1%) had a diagnosis of schizoaffective disorder, bipolar type, and 30.9% had the depressive type. The majority of subjects (82.9%) had a baseline YMRS score ≥ 16 (mean ± SD YMRS score = 25.7 ± 10.0), whereas 64.8% had a baseline HDRS-21 score ≥ 16 (mean ± SD HDRS-21 score = 20.1 ± 9.2) and 47.7% had both YMRS and HDRS-21 scores ≥ 16 at baseline. The 6-week completion rate was 77.0% in the higher-dose paliperidone ER group, 66.1% in the lower-dose group, and 58.9% in the placebo group (Figure 1). The most common reason for discontinuation from double-blind treatment was lack of efficacy; 20.6% of subjects in the placebo group, 9.0% in the paliperidone ER higher-dose group, and 11.0% in the lower-dose group discontinued.

The median duration of exposure to double-blind treatment was 43 days (ie, the planned length of double-blind treatment) in the paliperidone ER groups and 42 days in the placebo group. The majority (87.8%) of subjects in the higher-dose paliperidone ER group had a mode dose of 12 mg/d, and 89.5% of subjects in the lower-dose group had a mode dose of 6 mg/d. The mean ± SD modal daily dose of paliperidone ER was 11.6 ± 1.0 mg for the higher-dose group and 5.7 ± 0.9 mg for the lower-dose group. Overall, 13.3% of subjects in the higher-dose paliperidone ER group reduced their dose to 9 mg, and 12.4% of subjects in the lower-dose group reduced their dose to 3 mg during the first 15 days of the trial. In the ITT analysis set, 117 (37.7%) subjects were in the concomitant medication stratum and received mood stabilizers and/or antidepressants at baseline (placebo [n = 40], paliperidone ER higher-dose group [n = 39], paliperidone ER lower-dose group [n = 38]). Benzodiazepines were used in 57.0% of subjects in the placebo group, 55.1% in the paliperidone ER higher-dose group, and 61.0% in the lower-dose group.

Efficacy

PANSS total score. There was a significant improvement with higher-dose paliperidone ER compared with placebo

Table 1. Baseline Demographics and Characteristics (ITT analysis set)

Demographic	Placebo, n = 107	Lower-Dose Paliperidone ER, n = 105	Higher-Dose Paliperidone ER, n = 98
Gender, n (%)			
Male	67 (62.6)	70 (66.7)	64 (65.3)
Female	40 (37.4)	35 (33.3)	34 (34.7)
Age, mean (SD), y	37.1 (11.1)	38.1 (10.0)	36.5 (10.5)
Race, n (%)			
Asian	34 (31.8)	34 (32.4)	34 (34.7)
White	53 (49.5)	48 (45.7)	43 (43.9)
African American	20 (18.7)	23 (21.9)	20 (20.4)
American Indian or Alaska native	0	0	1 (1.0)
Other	0	0	0
Country, n (%)			
United States	39 (36.5)	39 (37.1)	35 (35.7)
India	33 (30.8)	34 (32.4)	31 (31.6)
Russia	12 (11.2)	13 (12.4)	11 (11.2)
Ukraine	23 (21.5)	19 (18.1)	21 (21.4)
	n = 106	n = 104	n = 97
Age at first psychiatric diagnosis, mean (SD), y	26.6 (10.6)	26.4 (10.2)	25.3 (9.4)
	n = 103	n = 105	n = 98
Age at first schizoaffective diagnosis, mean (SD), y	32.4 (11.3)	32.9 (10.3)	32.1 (10.4)
	n = 107	n = 104	n = 96
Diagnostic subtype of schizoaffective disorder, n (%)			
Depressive	33 (30.8)	35 (33.7)	27 (28.1)
Bipolar	74 (69.2)	69 (66.3)	69 (71.9)
	n = 103	n = 105	n = 98
Patients with schizoaffective chart diagnosis prior to screening, n (%)	97 (94.2)	91 (86.7)	88 (89.8)
	n = 104	n = 105	n = 96
Prior psychiatric diagnosis, n (%)[a]			
Schizophrenia	46 (44.2)	56 (53.3)	44 (45.8)
Bipolar disorder	36 (34.6)	29 (27.6)	30 (31.3)
Depression	18 (17.3)	19 (18.1)	16 (16.7)
	n = 105	n = 104	n = 97
Total psychiatric hospitalizations, mean (SD)	4.4 (5.9)	4.5 (6.3)	4.2 (5.1)
	n = 107	n = 105	n = 98
Baseline antidepressants or mood stabilizers, n (%)[a]			
Antidepressants	31 (29.0)	21 (20.0)	19 (19.4)
Mood stabilizers	30 (28.0)	30 (28.6)	31 (31.6)
Substance use, n (%)			
No	80 (74.8)	71 (67.6)	73 (74.5)
Yes	27 (25.2)	34 (32.4)	25 (25.5)
	n = 106	n = 108	n = 96
ISST score, n (%)[b]			
0	77 (72.6)	80 (74.1)	69 (71.9)
≥ 1	29 (27.4)	28 (25.9)	27 (28.1)
	n = 107	n = 105	n = 98
Attempted suicide, n (%)			
No	76 (71.0)	75 (71.4)	79 (80.6)
Yes	31 (29.0)	30 (28.6)	19 (19.4)
No. of attempts, n (%)			
1	19 (61.3)	16 (53.3)	11 (57.9)
≥ 2	12 (38.7)	14 (46.7)	8 (42.1)
PANSS total score, mean (SD)	91.6 (12.5)	95.9 (13.0)	92.7 (12.6)
CGI-S-SCA total score, mean (SD)	4.6 (0.6)	4.6 (0.6)	4.6 (0.6)
HDRS-21 score ≥ 16, n (%)	64 (59.8)	76 (72.4)	61 (62.2)
YMRS score ≥ 16, n (%)	90 (84.1)	88 (83.8)	79 (80.6)
Both HDRS-21 and YMRS scores ≥ 16, n (%)	47 (43.9)	59 (56.2)	42 (42.9)

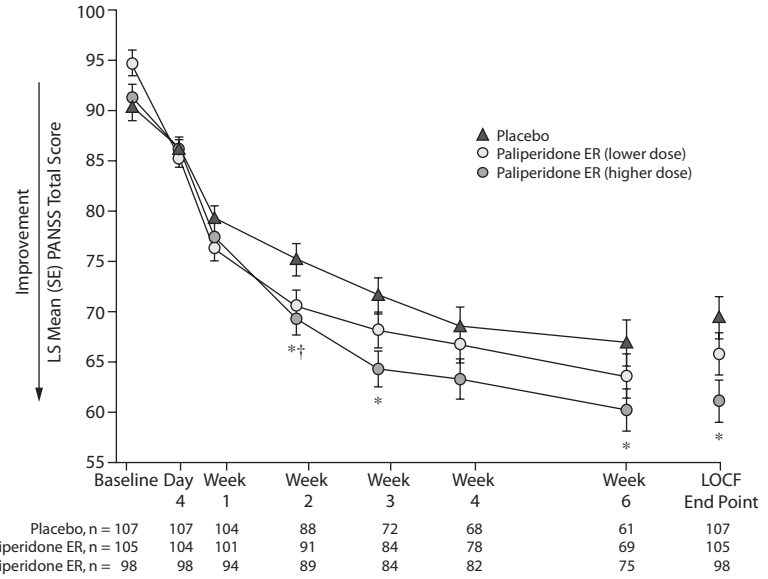
[a]Data are not mutually exclusive.
[b]Data from safety analysis set.
Abbreviations: CGI-S-SCA = Clinical Global Impressions-Severity of Illness Scale for Schizoaffective Disorder; ER = extended-release; HDRS-21 = Hamilton Depression Rating Scale, 21-item version; ISST = InterSePT Scale for Suicidal Thinking, ITT = intent to treat; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; YMRS = Young Mania Rating Scale.

in PANSS total score at week 6 LOCF end point: LS mean difference in change score was −8.3 (95% CI, −13.8 to −2.9) ($P = .003$). The lower-dose paliperidone ER group did not separate from placebo at the week 6 LOCF end point (−3.6 [95% CI, −9.0 to 1.8]; $P = .187$) (Figure 2, Table 2). The corresponding between-group effect sizes versus placebo were 0.42 for the higher-dose and 0.18 for the lower-dose paliperidone ER groups. No significant treatment-by-country ($P = .706$), treatment by region ($P = .855$), or treatment-by-concomitant medication stratum ($P = .641$) interactions were detected. Thus, the interaction assessment did not reveal a significant effect of these variables on the observed treatment effect.

Several post hoc subgroup analyses were also performed to further explore the impact of these variables on treatment effect (Figure 3). The point estimates showed a higher-dose paliperidone versus placebo effect in the subgroups that was consistent with the overall analysis in the total population. The study was not powered for these post hoc subgroup analyses, and the CIs cross the 0 line.

Using Mahalanobis distances, 8 outliers were identified (3 placebo, 3 lower dose, 2 higher dose). When these outliers were excluded from the primary outcome analysis, both the lower-dose (effect size 0.28; $P = .044$) and higher-dose paliperidone ER groups (effect size 0.54; $P < .001$) showed significant improvement versus placebo at the LOCF end point. The results using the repeated-measures ANCOVA model were also consistent with the primary analysis (Table 2). Subjects in the higher-dose paliperidone ER group had greater improvement in the PANSS total score compared with placebo ($P = .032$); there was no significant difference for the lower-dose group compared with placebo ($P = .286$). At week 6, the repeated-measures estimated differences from the placebo group were −6.7 for the

Figure 2. Mean PANSS Total Score Over Time (ITT analysis set)[a]



[a]Day 4 through week 6 based on observed scores using repeated-measures ANCOVA; LOCF end point comparison from an ANCOVA model.
*$P < .05$, higher-dose paliperidone ER vs placebo.
†$P < .05$, lower-dose paliperidone ER vs placebo.
Abbreviations: ANCOVA = analysis of covariance, ER = extended-release, ITT = intent to treat, LOCF = last observation carried forward, LS = least squares, PANSS = Positive and Negative Syndrome Scale, SE = standard error.

higher-dose paliperidone ER group and –3.3 for the lower-dose group.

Other efficacy analyses. There were significant improvements with higher-dose paliperidone ER compared with placebo for the positive ($P = .001$), disorganized thoughts ($P = .004$), and uncontrolled hostility/excitement ($P < .001$) PANSS factor scores. The lower-dose paliperidone ER group did not separate from placebo on any of the factor scores at the week 6 LOCF end point (Table 2). A significantly greater proportion of subjects were composite responders in both the lower-dose (56.7%; $P = .008$) and higher-dose (62.2%; $P = .001$) paliperidone ER groups compared with the placebo group (40.2%). A significant difference ($P = .026$) was noted in the time to first composite response between the higher-dose paliperidone ER group and the placebo group.

The higher-dose, but not lower-dose, paliperidone ER group exhibited significant improvements versus placebo in mean CGI-S-SCA total score ($P < .001$), as well as CGI-S-SCA positive ($P < .001$), negative ($P = .038$), and manic ($P < .001$) domain scores (Table 3). For subjects with prominent manic symptoms at baseline (YMRS ≥ 16), the higher-dose (but not lower-dose) group demonstrated a significant improvement ($P < .001$) versus placebo in the total YMRS score (Table 3). For those with prominent depressive symptoms at baseline (HDRS-21 ≥ 16), both the higher-dose and lower-dose groups showed a significant improvement ($P < .05$) in total HDRS-21 scores versus placebo. Consistent with these analyses, higher-dose paliperidone ER was effective in improving PANSS total score regardless of baseline affective symptomatology (Figure 3). For the secondary endpoints, the results of the repeated-measures ANCOVA model were largely consistent with the LOCF analyses, with the exception of CGI-S-SCA negative domain score and the HDRS-21 total score. These scores both showed significant differences between higher-dose paliperidone ER and placebo with the LOCF analyses but not with the repeated-measures model (Table 3).

Safety

Overall, 69.4% of the higher-dose paliperidone ER group, 72.2% of the lower-dose group, and 57.0% of the placebo group experienced at least 1 treatment-emergent adverse event. Across treatment groups, most adverse events were mild or moderate in severity. The most common adverse events are reported in Table 4 and, for the paliperidone ER groups, included headache, nausea, and insomnia. A higher percentage of subjects in the lower-dose paliperidone ER group (9.3%) experienced treatment-emergent serious adverse events (SAEs) compared with the placebo (5.6%) or higher-dose paliperidone ER (2.0%) groups. The majority of the SAEs were related to exacerbation of the underlying illness. Four subjects had SAEs that the investigator considered at least possibly related to the study drug. These included 1 case of suicidal ideation and 1 case of supraventricular tachycardia in the placebo group, and 1 case of depressed mood and 1 case of psychotic disorder in the lower-dose paliperidone ER group. No subject died during the study. Discontinuation rates due to adverse events were 4.1% in the higher-dose paliperidone ER group, 9.5% in lower-dose group, and 6.5% in the placebo group.

Extrapyramidal symptom (EPS)–related adverse events were reported in 22.4% of those in the paliperidone ER higher-dose group, in 23.1% in the lower-dose group, and in 12.1% in the placebo group. The most common EPS-related adverse events (higher-dose paliperidone ER group, lower-dose group, and placebo group, respectively) were tremor (11.2%, 12.0%, 3.7%), akathisia (6.1%, 3.7%, 7.5%), and hypertonia (4.1%, 8.3%, 2.8%). The changes in EPS rating scale scores (SAS, BAS, AIMS) at week 6 and week 6 LOCF were similar and low across the treatment groups; median scores were all < 1 at all time points. There were no reported acute events of extrapyramidal disorder or tardive dyskinesia during the study. Eighteen (18.4%) subjects in the higher-dose group, 15 (14.3%) in the lower-dose group, and 14 (13.1%)

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Table 2. PANSS Total and Factor Scores (ITT analysis set)

PANSS Score	Placebo (n = 107)	Lower-Dose Paliperidone ER (n = 105)	Higher-Dose Paliperidone ER (n = 98)
Total			
LOCF analysis[a]			
Baseline score, mean (SD)	91.6 (12.5)	95.9 (13.0)	92.7 (12.6)
Score change at end point (ANCOVA), LS mean (SE)	−24.1 (2.1)	−27.7 (2.1)	−32.4 (2.1)
P value vs placebo	…	.187	.003
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−26.8 (2.3)[c]	−30.1 (2.2)[d]	−33.5 (2.1)[e]
P value vs placebo	…	.286	.032
Positive symptoms factor			
LOCF analysis[a]			
Baseline score, mean (SD)	27.0 (5.1)	27.6 (5.0)	27.0 (5.2)
Score change at end point (ANCOVA), LS mean (SD)	−7.3 (0.7)	−8.4 (0.7)	−10.2 (0.7)
P value vs placebo	…	.209	.001
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−8.4 (0.7)[c]	−9.1 (0.7)[d]	−10.8 (0.7)[e]
P value vs placebo	…	.475	.015
Negative symptoms factor			
LOCF analysis[a]			
Baseline score, mean (SD)	17.9 (5.7)	19.6 (6.0)	18.4 (5.6)
Score change at end point (ANCOVA), LS mean (SE)	−3.6 (0.5)	−4.2 (0.5)	−4.3 (0.5)
P value vs placebo	…	.310	.232
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−4.1 (0.5)[c]	−4.9 (0.5)[d]	−4.5 (0.5)[e]
P value vs placebo	…	.266	.548
Anxiety/depression factor			
LOCF analysis[a]			
Baseline score, mean (SD)	12.7 (4.0)	13.4 (3.5)	12.7 (3.7)
Score change at end point (ANCOVA), LS mean (SD)	−3.8 (0.3)	−4.6 (0.3)	−4.6 (0.3)
P value vs placebo	…	.099	.071
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−4.4 (0.4)[c]	−5.0 (0.4)[d]	−4.6 (0.4)[e]
P value vs placebo	…	.223	.675
Disorganized thoughts factor			
LOCF analysis[a]			
Baseline score, mean (SD)	19.6 (4.0)	20.7 (4.1)	19.9 (3.8)
Score change at end point (ANCOVA), LS mean (SD)	−4.2 (0.5)	−4.9 (0.5)	−6.0 (0.5)
P value vs placebo	…	.269	.004
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−5.1 (0.5)[c]	−5.6 (0.5)[d]	−6.4 (0.5)[e]
P value vs placebo	…	.498	.060
Uncontrolled hostility/excitement factor			
LOCF analysis[a]			
Baseline score, mean (SD)	14.5 (3.0)	14.7 (2.9)	14.7 (2.9)
Score change at end point (ANCOVA), LS mean (SE)	−5.1 (0.4)	−5.6 (0.4)	−7.2 (0.4)
P value vs placebo	…	.314	< .001
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−5.7 (0.5)[c]	−6.1 (0.4)[d]	−7.4 (0.4)[e]
P value vs placebo	…	.499	.005

[a]Between-treatment-group comparisons are from an ANCOVA model with fixed effects for treatment, concomitant medication stratum, and country, and baseline value as a covariate.
[b]Between-treatment-group comparisons are based on observed scores using a repeated-measures ANCOVA model with baseline score as a covariate; treatment, country, concomitant medication stratum, and time as fixed-effect factors; and the treatment-by-time interaction.
[c]n = 61.
[d]n = 69.
[e]n = 75.
Abbreviations: ANCOVA = analysis of covariance, ER = extended-release, ITT = intent to treat, LOCF = last observation carried forward, LS = least squares, PANSS = Positive and Negative Syndrome scale, SD = standard deviation, SE = standard error.

in the placebo group received concomitant anti-EPS medication. The majority of subjects in all 3 treatment groups had a baseline ISST score of 0 (Table 1), and nonsignificant decreases from baseline in ISST suicidality scores were observed in all 3 groups at week 6 and week 6 LOCF.

There were increases in mean ± SD body weight in all groups from baseline to week 6 and week 6 LOCF; the magnitude of the increase was greater in the paliperidone ER groups compared with the placebo group at both time points (week 6 LOCF: placebo group, 0.3 ± 2.0 kg; paliperidone ER lower-dose group, 1.2 ± 2.7 kg; paliperidone ER higher-dose group, 1.4 ± 2.7 kg) (Table 5). At week 6 LOCF, the number and percentages of patients who had > 7% increases in body weight were 7 (7.1%) in the paliperidone ER higher-dose group, 3 (2.9%) in the lower-dose group, and 1 (0.9%) the placebo group. Elevations in prolactin levels were observed at week 6 LOCF in both paliperidone ER groups (Table 5). Four subjects had potentially prolactin-related adverse events: 1 subject each in the placebo and paliperidone ER higher-dose groups had anorgasmia (the placebo subject also had libido decreased), 1 subject in the lower-dose paliperidone ER group had erectile dysfunction, and 1 subject in the higher-dose paliperidone ER group had breast pain and galactorrhea. At week 6 LOCF, the incidence of treatment-emergent markedly abnormal laboratory chemistry and hematology test values was greater in the placebo group than in the paliperidone ER dose groups (laboratory chemistry: placebo group, 12.2%; paliperidone ER lower-dose group, 6.7%; paliperidone ER higher-dose group, 7.9%; and hematology: placebo group, 7.1%; paliperidone ER lower-dose group, 5.6%; paliperidone ER higher-dose group, 2.3%). One subject in the higher-dose paliperidone ER group had a markedly abnormal elevation in alanine aminotransferase, and 1 subject in the lower-dose paliperidone ER group had a markedly abnormal elevation in fasting glucose. No subject in any treatment group had abnormal ECG findings.

DISCUSSION

Few controlled clinical trials have studied treatments specifically for patients with schizoaffective disorder. This international, double-blind, placebo-controlled trial of paliperidone ER is part of the first registration program to evaluate the efficacy and safety of an antipsychotic medication in patients with this condition. Greater clinical improvement was observed with higher-dose paliperidone ER versus placebo on the primary

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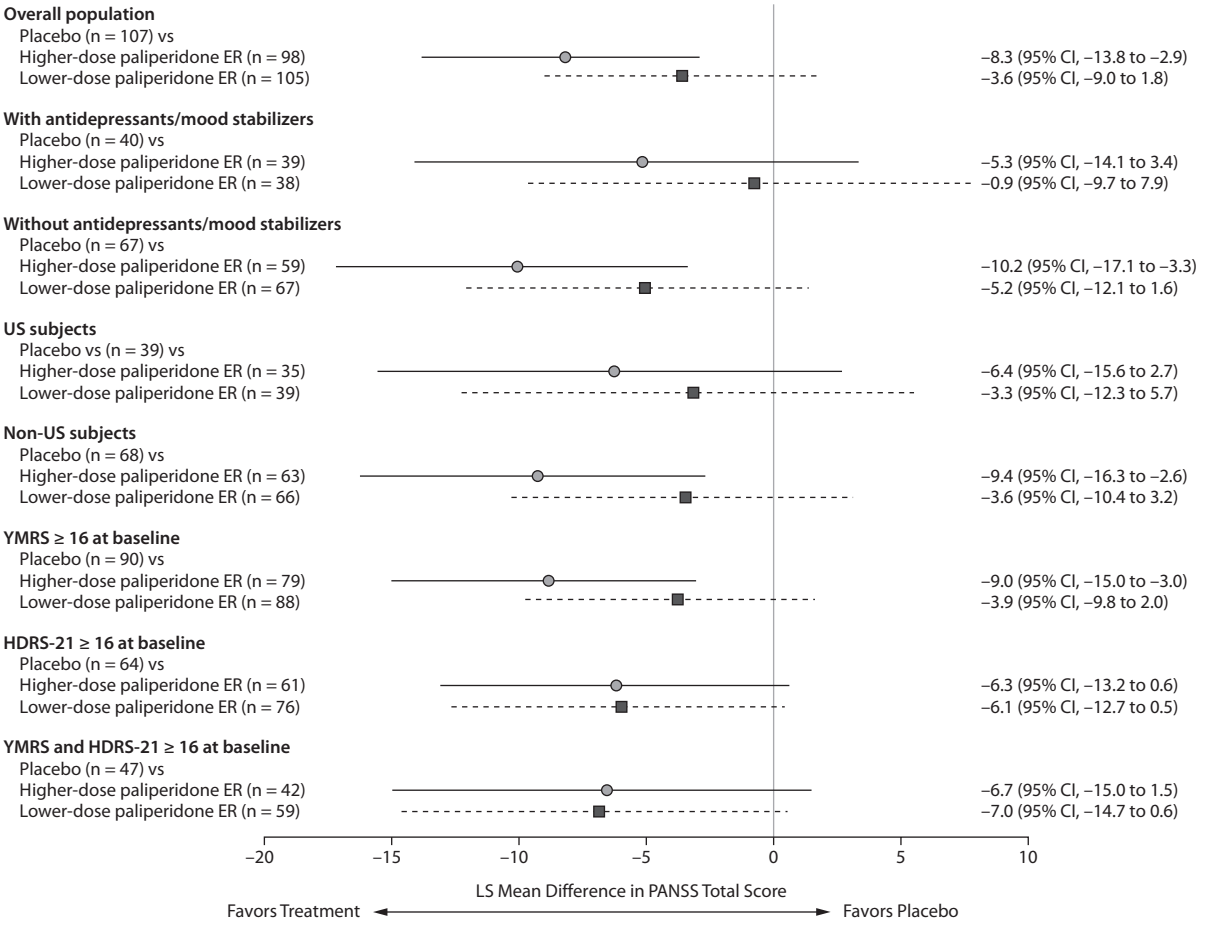
Figure 3. Differences in PANSS Total Change Scores at End Point With Paliperidone ER Versus Placebo Overall and by Strata and Subgroups (ITT Analysis Set, Last Observation Carried Forward)



Abbreviations: ER = extended-release; HDRS-21 = Hamilton Depression Rating Scale, 21-item version; ITT = intent to treat; PANSS = Positive and Negative Syndrome Scale; YMRS = Young Mania Rating Scale.

outcome parameter, change in PANSS total score. The observed between-group effect size of 0.42 and the magnitude of PANSS total change (–32.4 points versus baseline) are considered clinically meaningful.[24,25] Higher-dose paliperidone ER was also superior to placebo on most secondary efficacy measures, including PANSS positive score, disorganized thought and hostility/excitement factors, composite response rates, the overall CGI-S-SCA scale, and the CGI-S-SCA positive, negative, and manic domains. Additionally, higher-dose paliperidone ER was more effective than placebo in reducing manic and depressive symptoms in patients with prominent affective symptomatology. Although lower-dose paliperidone ER was not statistically superior to placebo on the change in mean PANSS total score, this dosage group did show significantly greater composite response rates and greater reduction in depressive symptoms versus placebo in patients with prominent depressive symptomatology.

The baseline clinical characteristics of the population recruited to this study reflected marked psychotic symptoms coupled with prominent affective symptoms and are consistent with the distinctive profile of patients with schizoaffective disorder.[3] In addition to the requirement of a SCID-confirmed diagnosis of schizoaffective disorder, the inclusion criteria were designed to ensure that subjects were experiencing an acute psychotic exacerbation along with prominent affective symptomatology. Indeed, the observed mean baseline PANSS scores in the low- to mid-90s reflect the acutely psychotic nature of the population, and the mean baseline YMRS and HDRS-21 scores were well above the threshold set by the entry criteria. At baseline, over 80% of the population had prominent manic symptomatology, approximately two-thirds of the subjects had prominent depressive symptoms, and slightly fewer than half had both prominent manic and depressive symptomatology.

In this population with a high level of psychosis and a predominance of manic symptoms, the higher-dose paliperidone ER was required for the full range of treatment effect. In the companion schizoaffective disorder study (which used a flexible-dose design), paliperidone ER was

Table 3. Secondary Efficacy Endpoints (ITT analysis set)

Variable	Placebo (n = 107)	Lower-Dose Paliperidone ER (n = 105)	Higher-Dose Paliperidone ER (n = 98)
CGI-S-SCA Score			
Total severity score			
LOCF analysis[a]			
Baseline, mean (SD)	4.6 (0.6)	4.6 (0.6)	4.6 (0.6)
Score change at end point (ANCOVA), LS mean (SE)	−1.3 (0.1)	−1.5 (0.1)	−1.9 (0.1)
P value vs placebo	…	.083	< .001
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−1.6 (0.1)	−1.7 (0.1)	−1.9 (0.1)
P value vs placebo	…	.517	.027
Positive domain score			
LOCF analysis[a]			
Baseline, mean (SD)	4.5 (0.6)	4.5 (0.7)	4.6 (0.6)
Score change at end point (ANCOVA), LS mean (SE)	−1.3 (1.3)	−1.5 (1.3)	−1.9 (1.2)
P value vs placebo	…	.212	< .001
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−1.7 (0.1)	−1.8 (0.1)	−2.1 (0.1)
P value vs placebo	…	.762	.013
Negative domain score			
LOCF analysis[a]			
Baseline, mean (SD)	3.0 (1.1)	3.4 (1.0)	3.2 (1.0)
Score change at end point (ANCOVA), LS mean (SE)	−0.5 (0.9)	−0.7 (1.0)	−0.8 (1.1)
P value vs placebo	…	.430	.038
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−0.7 (0.1)	−0.8 (0.1)	−0.9 (0.1)
P value versus placebo	…	.406	.163
Depressive domain score			
LOCF analysis[a]			
Baseline, mean (SD)	3.0 (1.5)	3.2 (1.5)	3.1 (1.6)
Score change at end point (ANCOVA), LS mean (SE)	−0.7 (1.3)	−1.0 (1.6)	−0.9 (1.3)
P value vs placebo	…	.208	.201
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−0.8 (0.1)	−1.0 (0.1)	−1.0 (0.1)
P value vs placebo	…	.356	.547
Manic domain score			
LOCF analysis[a]			
Baseline, mean (SD)	3.6 (1.5)	3.5 (1.6)	3.6 (1.5)
Score change at end point (ANCOVA), LS mean (SE)	−0.9 (1.4)	−1.1 (1.5)	−1.6 (1.4)
P value vs placebo	…	.155	< .001
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−1.2 (0.1)	−1.2 (0.1)	−1.7 (0.1)
P value vs placebo	…	.822	.014
Patients exhibiting prominent manic symptoms (YMRS ≥ 16)			
YMRS total score			
LOCF analysis[a]	n = 90	n = 88	n = 79
Baseline, mean (SD)	28.5 (6.9)	28.4 (7.4)	29.9 (8.2)
Score change at end point (ANCOVA), LS mean (SE)	−13.4 (1.2)	−16.2 (1.2)	−20.2 (1.2)
P value (treatment vs placebo)	…	.066	< .001
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−14.0 (1.4)	−15.9 (1.3)	−21.0 (1.4)
P value vs placebo	…	.322	< .001
Patients exhibiting prominent depressive symptoms (HDRS-21 ≥ 16)			
HDRS-21 total score			
LOCF analysis[a]	n = 64	n = 76	n = 61
Baseline, mean (SD)	24.4 (5.9)	25.2 (6.8)	26.9 (7.3)
Score change at end point (ANCOVA), LS mean (SE)	−10.5 (1.3)	−14.3 (1.2)	−13.9 (1.3)
P value (treatment vs placebo)	…	.013	.032
Repeated-measures ANCOVA[b]			
Model estimate for week 6 (SE)	−12.9 (1.3)	−15.6 (1.1)	−15.0 (1.2)
P value vs placebo	…	.099	.220

[a]Between-treatment-group comparisons are from an ANCOVA model with fixed effects for treatment, concomitant medication stratum, and country; and baseline value as a covariate.
[b]Between-treatment-group comparisons are based on observed scores using a repeated-measures ANCOVA model with baseline score as a covariate; treatment, country, concomitant medication stratum, and time as fixed-effect factors; and the treatment-by-time interaction.
Abbreviations: ANCOVA = analysis of covariance; CGI-S-SCA = Clinical Global Impressions-Severity of Illness Scale for Schizoaffective Disorder; ER = extended-release; HDRS-21 = Hamilton Depression Rating Scale, 21-item version; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error; YMRS = Young Mania Rating Scale.

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Table 4. Adverse Events (≥5% in any treatment group) (safety analysis set)

Adverse Event, n (%)	Placebo (n = 107)	Lower-Dose Paliperidone ER (n = 108)	Higher-Dose Paliperidone ER (n = 98)
At least 1 adverse event	61 (57.0)	78 (72.2)*	68 (69.4)
Headache	18 (16.8)	15 (13.9)	13 (13.3)
Tremor	4 (3.7)	13 (12.0)*	11 (11.2)
Insomnia	9 (8.4)	5 (4.6)	9 (9.2)
Nausea	8 (7.5)	9 (8.3)	8 (8.2)
Somnolence	2 (1.9)	5 (4.6)	8 (8.2)
Dyspepsia	0 (0.0)	5 (4.6)	6 (6.1)*
Akathisia	8 (7.5)	4 (3.7)	6 (6.1)
Constipation	2 (1.9)	4 (3.7)	5 (5.1)
Nasopharyngitis	2 (1.9)	2 (1.9)	5 (5.1)
Hypertonia	3 (2.8)	9 (8.3)	4 (4.1)
Sedation	5 (4.7)	8 (7.4)	4 (4.1)
Dizziness	7 (6.5)	6 (5.6)	4 (4.1)
Dry mouth	4 (3.7)	7 (6.5)	2 (2.0)
Agitation	6 (5.6)	7 (6.5)	1 (1.0)
Schizoaffective disorder[a]	3 (2.8)	6 (5.6)	0 (0.0)

[a]Verbatim adverse events reported by the investigators that were coded to this term were worsening of schizoaffective disorder, acute exacerbation of schizoaffective disorder, decompensation of schizoaffective disorder, and exacerbation of schizoaffective symptoms.
*$P < .05$, treatment versus placebo without correction for multiplicity (Fisher exact test).
Abbreviation: ER = extended-release.

Table 5. Laboratory Analyses of Interest (safety analysis set)

Variable	Placebo (n = 107)	Lower-Dose Paliperidone ER (n = 108)	Higher-Dose Paliperidone ER (n = 98)
Weight, mean ± SD, kg			
Baseline	80.0 ± 22.0	74.4 ± 20.1	78.4 ± 23.0
Change from baseline to week 6 LOCF	0.3 ± 2.0	1.2 ± 2.7	1.4 ± 2.7
Prolactin, mean ± SD, ng/mL			
Baseline			
Male	15.0 ± 15.4	15.5 ± 13.6	15.4 ± 15.7
Female	33.3 ± 33.4	44.0 ± 54.4	42.5 ± 57.3
Change from baseline to week 6 LOCF			
Male	−4.8 ± 14.8	8.0 ± 16.6	14.5 ± 24.0
Female	−11.8 ± 36.0	37.8 ± 69.4	48.8 ± 54.0
Subjects (male and female) who shifted from normal prolactin levels at baseline to high prolactin levels at week 6 LOCF, %[a]	6.7	41.1	43.8
Fasting glucose, mean ± SD, mg/dL			
Baseline	91.8 ± 14.7	90.5 ± 15.1	94.6 ± 25.0
Change from baseline to week 6 LOCF	2.2 ± 26.5	9.3 ± 26.9	2.0 ± 27.8
HDL-C, mean ± SD, mg/dL			
Baseline	45.8 ± 12.2	49.3 ± 13.6	47.8 ± 13.8
Change from baseline to week 6 LOCF	−0.8 ± 10.4	0.5 ± 10.5	1.6 ± 10.1
LDL-C, mean ± SD, mg/dL			
Baseline	103.1 ± 30.6	96.5 ± 38.4	104.4 ± 38.5
Change from baseline to week 6 LOCF	2.6 ± 23.2	−0.5 ± 26.3	3.0 ± 24.9
Triglycerides, mean ± SD, mg/dL			
Baseline	130.0 ± 75.6	130.5 ± 73.9	137.7 ± 84.4
Change from baseline to week 6 LOCF	6.3 ± 74.8	4.1 ± 77.2	−4.6 ± 70.2

[a]Normal ranges for prolactin: male, 2–20 ng/mL; female, 2–29 ng/mL.
Abbreviations: ER = extended-release, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LOCF = last observation carried forward, SD = standard deviation.

found to be significantly more effective than placebo at a mean mode dose of 8.6 mg/d.[15] Importantly, interpretation of optimal dosing is limited in that this is not a true dose-finding study; there were 2 paliperidone ER groups, each of which allowed a narrow range of doses. Additionally, a post hoc analysis from this study, excluding data from the 8 identified outliers, found that both the lower- and higher-dose paliperidone ER were significantly different from placebo ($P = .044$ and $P < .001$, respectively) in the change from baseline in PANSS total score at the LOCF end point, suggesting that many patients with schizoaffective disorder may benefit from the lower doses of paliperidone ER.

Despite the large proportion of subjects with prominent manic and mixed symptomatology, the population appeared to respond to higher-dose paliperidone ER used both as monotherapy and as an adjunct to mood stabilizers and/or antidepressants. Although the study itself was neither powered nor designed to assess the relative effect of paliperidone ER as monotherapy or as an adjunct to other medications, qualitatively similar outcomes were observed in patients who did and did not receive concomitant medications. This observation is relevant to clinical practice, where combination therapy for schizoaffective disorders is common.[6] Further, because paliperidone ER is not extensively metabolized by the liver, it may be less likely than other antipsychotics to be associated with significant drug-drug interactions when used as an adjunct to other psychotropics.[26]

Also of note in this study was the high placebo response, with a mean ± SE 24.1 ± 2.1–point reduction in mean PANSS score in subjects receiving placebo and 40.2% of the placebo group achieving composite response at end point. Although benzodiazepine use can contribute to placebo response, the frequency of benzodiazepine exposure was comparable across treatment groups (placebo: 48.6%; paliperidone ER: lower-dose group, 52.4%; paliperidone ER higher-dose group, 44.9%). Although a large placebo effect might be attributed to a feature of schizoaffective disorder per se, this degree of placebo response was not observed in a companion study in a schizoaffective disorder population.[15] Of late, increasingly large placebo responses have beset signal detection in clinical drug trials in mood and psychotic disorders,[27] and trials < 6 to 8 weeks in duration appear to be particularly vulnerable.[27] This high placebo

response may have obscured the significant efficacy measures for the lower-dose group.

The change in PANSS score was selected as the primary outcome parameter in this registration program. Although the PANSS has traditionally been used in schizophrenia treatment trials, content mapping of PANSS items with *DSM-IV* diagnostic criteria shows that the PANSS covers the majority of items related to schizophrenia as well as key symptoms of mania and major depressive disorder. Moreover, the PANSS has been shown to have good reliability and sensitivity to change in combined schizophrenia and schizoaffective disorder populations and in the few small studies conducted specifically in populations with schizoaffective disorder.[28–30]

In addition to the PANSS, this study employed the novel CGI-S-SCA and CGI-C-SCA scales, specifically developed for this program, which evaluate the 4 main domains of schizoaffective disorder: positive, negative, manic, and depressive. In this trial, the CGI-SCA was sensitive to improvement in positive, negative, and manic domains. Ongoing scale validation indicates strong correlations (Spearman correlations coefficients > 0.6) for each of the CGI-SCA domains and their corresponding symptom-based scale measures (ie, PANSS positive and negative subscales, YMRS, and HDRS-21).[19]

Safety findings—including those related to movement disorders, weight and metabolic effects, and hyperprolactinemia—were generally similar to those reported in studies of paliperidone ER in patients with schizophrenia.[8–11] There were higher rates of EPS-related tremor with both paliperidone ER dose groups. However, no clear dose-dependent effects in other measures of movement disorders were observed. Mean prolactin levels were higher in subjects who received paliperidone ER than in placebo (as anticipated, the magnitude of elevation was greater in women), yet few patients experienced potentially prolactin-related adverse events. Weight gain was greater with active treatment than with placebo. Notably, the incidence of treatment-emergent SAEs was greater in the lower-dose paliperidone ER group (9.3%) than in the placebo (5.6%) and higher-dose paliperidone ER (2.0%) groups. Within the 10 lower-dose paliperidone ER group subjects who experienced an SAE, 8 events were psychiatric and likely related to insufficient response. Likewise, the frequency of adverse events leading to discontinuation was higher in the lower-dose paliperidone ER group (9.3%) compared with the placebo (7.5%) and higher-dose group (3.1%), with the majority of these events related to a psychiatric disorder. These results are consistent with the efficacy findings, suggesting the need for higher dosing to achieve optimal treatment response in most acutely ill patients with schizoaffective disorder.

Finally, the generalizability of the study findings may be limited by some of the inclusion criteria. Although patients with schizoaffective disorder are at increased risk for suicide,[2] those with a history of a suicide attempt within the last year and those at imminent risk of suicide were excluded from the trial. Patients with schizoaffective disorder are also at risk for substance abuse.[1] Even though this was not exclusionary, less than 30% of subjects reported a history of substance use.

In summary, this study indicates that paliperidone ER is effective in the acute treatment of the range of psychotic and affective symptoms characteristic of schizoaffective disorder, particularly in patients with prominent positive and/or manic symptoms. Further, no new safety signal was detected in this population of patients. Findings from this study are consistent with results from a companion study,[15] which together form the basis of the first registration program and US Food and Drug Administration approval in schizoaffective disorder.

Drug names: benztropine (Cogentin and others), carbamazepine (Carbatrol, Equetro, and others), lorazepam (Ativan and others), paliperidone (Invega).

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