Efficacy and Tolerability of Oral Paliperidone Extended-Release Tablets in the Treatment of Acute Schizophrenia: Pooled Data From Three 6-Week, Placebo-Controlled Studies

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Objective: To evaluate the efficacy and safety of an extended-release (ER) formulation of paliperidone in patients with an acute episode of schizophrenia, in the dosage range of 3 to 15 mg daily.

Method: A pooled analysis of 3 similarly designed 6-week, multicenter, double-blind, randomized, fixed-dose, placebo-controlled studies in 1326 patients with acute schizophrenia (Positive and Negative Syndrome Scale [PANSS] total score of 70–120) was performed. Patients were randomly assigned to receive 3, 6, 9, 12, or 15 mg daily of paliperidone ER or placebo. Efficacy and safety assessments were performed. The primary endpoint was change in PANSS total score from baseline to endpoint.

Results: PANSS total, PANSS subscale factor, and Personal and Social Performance scale scores significantly improved at endpoint for all doses of paliperidone ER relative to placebo ($p \leq .001$). A significantly greater proportion of paliperidone ER–treated patients at all doses achieved a clinical response compared with placebo ($p \leq .001$). Treatment-emergent adverse events (TEAEs) occurred in 66% to 77% of patients in the paliperidone ER groups and 66% of patients in the placebo group; serious TEAEs occurred in 6% of patients who received placebo and 5% to 6% of paliperidone ER–treated patients. Regardless of treatment group, median Simpson-Angus Rating Scale global, Abnormal Involuntary Movement Scale total, and Barnes Akathisia Rating Scale scores were 0 at both baseline and endpoint. There were no clinically relevant differences in measures of body weight gain, glucose handling, lipid metabolism, or proportion of patients with abnormal corrected QT intervals on electrocardiography and no important differences between the proportion of patients who received paliperidone ER or placebo who reported potentially glucose- or prolactin-related events.

Conclusions: Paliperidone ER given once daily for 6 weeks appears to be a safe, well-tolerated, and effective treatment for patients with acute schizophrenia.

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Antipsychotic drugs represent the main treatment for schizophrenia. When the efficacy of pharmacologic treatment is optimized by choosing the appropriate dose and duration of treatment, and avoiding polypharmacy, and combined with various types of psychosocial treatments, significant improvement in treating positive and negative symptoms, cognitive impairment, and quality of life is often possible.[1–3] However, even in patients in whom this has been achieved, functional improvement, in terms of work and social function, has been more elusive, with the vast majority of patients with schizophrenia being unable to live independently or obtain and hold paid employment.[4] Furthermore, there are serious limitations for some antipsychotic drugs with regard to side effect burden, particularly high levels of extrapyramidal symptoms (EPS) and risk for tardive dyskinesia with the typical

antipsychotic drugs,[5] and risk for metabolic adverse effects[6] with some but not all atypical antipsychotic drugs. Adherence with oral medication is known to be poor for many patients with schizophrenia, reflecting limitations in efficacy and tolerability, as well as lack of insight.[7] These considerations establish the need for the continued development of safe and tolerable pharmacologic treatments for schizophrenia that are more efficacious in alleviating the psychopathology and cognitive impairment of schizophrenia, which would be expected to lead to improved quality of life, work and social function, and adherence. The recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[8] study and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS)[9] support these general conclusions, although they have more negative views with regard to the efficacy of antipsychotic drugs in general.

Paliperidone (9-OH-risperidone) is the major active metabolite of risperidone, one of the most commonly used atypical antipsychotic medications. Paliperidone has been developed as a separate antipsychotic drug. Risperidone and paliperidone have similar binding affinities for receptor subgroups believed to be important in the treatment of schizophrenia and related disorders. Paliperidone fits several preclinical models of an atypical antipsychotic drug, including high affinity binding to both D_2 and 5-HT_{2A} receptors (favoring 5-HT_{2A} at relevant concentrations)[10,11] and high dissociation rate from human cloned D_2 receptor.[12] An extended-release (ER) formulation for paliperidone has been developed and approved in several markets that allows gradually ascending release of the drug over 24 hours in single doses and may result in small 24-hour peak-to-trough fluctuations in plasma paliperidone levels at steady state and in lower plasma concentrations of the drug to achieve desired D_2 occupancy levels[13] compared with immediate-release oral formulations. Such a profile may predict improved tolerability for concentration-dependent adverse effects, particularly EPS. Paliperidone undergoes only limited hepatic metabolism[14] and may thus avoid potential hepatic drug-drug or drug-disease interactions. Paliperidone palmitate, a long-acting injectable formulation of paliperidone, is currently in development.

The efficacy, safety, and tolerability of paliperidone ER for the acute phase treatment of schizophrenia have been established on the basis of results from three 6-week placebo-controlled studies of similar design.[15–17] We present the results of a pooled data analysis from these 3 studies.

METHOD

Sample and Treatment

This was a pooled analysis of 3 similarly designed 6-week, international multicenter, double-blind, randomized, fixed-dose, placebo-controlled phase 3 studies of paliperidone ER in patients with acute schizophrenia. In each study, patients (age ≥ 18 years) who were experiencing an acute episode of schizophrenia (defined as a Positive and Negative Syndrome Scale [PANSS] total score of 70–120) and could provide written informed consent were enrolled from 23 different countries on 5 continents. The first 2 weeks of each study consisted of an inpatient protocol-driven hospitalization. In each study, patients were randomly assigned to 1 of 5 paliperidone ER active treatment groups (3, 6, 9, 12, or 15 mg daily) or placebo. For each of the 6-week phase 3 studies, an olanzapine treatment arm (10 mg daily) was included as a positive control in order to confirm the assay sensitivity of each study. The olanzapine arms in each of these studies were not individually powered to detect differences in treatment efficacy between paliperidone ER and olanzapine. However, the large dataset generated by combining studies in the manner described above permitted some meaningful comparisons between olanzapine treatment at 10 mg daily and paliperidone ER across the 3- to 15-mg daily dosage range.

Patients were assessed on all outcome measures (outlined below) at baseline and on study days 4 and 8 and weekly thereafter through day 43. Studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Reporting Practice. The final study protocols were reviewed and approved by independent institutional review boards. Written informed consent was obtained from each patient.

Efficacy Assessments

For each of the studies, the primary efficacy measure was the change from baseline to endpoint in PANSS total scores for each paliperidone ER dose versus placebo in the intent-to-treat (ITT) analysis set, which consisted of patients who received at least 1 dose of double-blind study medication and had at least 1 follow-up assessment. Secondary outcome measures for efficacy included PANSS subscale factor (positive symptom, negative symptom, disorganization, hostility/excitement, and anxiety/depression) scores and Clinical Global Impressions-Severity of Illness scale (CGI-S) scores. Clinicians who provided the clinical ratings were blind to the assigned treatment of study patients.

Clinical efficacy for personal and social functioning was assessed using the Personal and Social Performance (PSP) scale.[18] The PSP scale is a clinician-rated instrument consisting of a 100-point single-item rating scale, subdivided into 10 equal intervals. Scores of 1 to 10 indicate lack of autonomy in basic functioning, whereas scores in the 91- to 100-point range reflect excellent functioning. The scale items were designed to assess 4 primary domains: (1) socially useful activities (including work and study), (2) personal and social relationships, (3) self-care, and (4) disturbing and aggressive behaviors. In

Table 1. Demographic and Clinical Baseline Characteristics

Characteristic	Placebo (N = 351)	Paliperidone ER 3 mg (N = 123)	6 mg (N = 234)	9 mg (N = 245)	12 mg (N = 240)	15 mg (N = 113)
Age, y[a]	39 (11.0)	36.3 (11.0)	39.4 (10.5)	37.4 (11.2)	38.5 (11.0)	37.6 (9.8)
Sex, %						
Male	66	63	59	62	61	65
Female	34	37	41	38	39	35
Race, %						
White	62	50	65	69	65	44
Black	23	20	27	9	27	24
Asian	8	24	0	11	0	26
Other	8	6	8	10	8	6
Weight, kg[a]	78.3 (20.0)	73.9 (19.9)	78.9 (19.6)	72.1 (16.4)	78.3 (20.4)	77.3 (24.1)
PANSS[a] total score	93.9 (11.7)	91.6 (12.2)	93.4 (11.2)	93.6 (12.6)	94.4 (11.2)	92.3 (12.3)
PSP[a] scale score	48.1 (13.8)	48.4 (13.7)	46.8 (13.6)	49.0 (15.2)	46.0 (13.7)	47.9 (14.8)

[a]Mean (standard deviation); intent-to-treat population.
Abbreviations: ER = extended-release, PANSS = Positive and Negative Syndrome Scale, PSP = Personal and Social Performance.

patients with acute schizophrenia, an improvement of ≥ 1 10-point category represents a clinically meaningful difference.[19]

Categorical treatment response was defined a priori in 2 ways. The first of these was a ≥ 30% decrease in PANSS total scores from baseline to endpoint (i.e., a symptom-based response criterion). The second was a function-based criterion defined as an improvement of at least one 10-point PSP category.

Safety and Tolerability Assessments

Safety assessments included reporting of spontaneous adverse events. Clinical evaluations performed at baseline and study endpoint included fasting blood glucose, body weight, fasting lipids, and electrocardiogram (ECG). Prolactin concentrations were also measured at baseline and endpoint in all studies. Extrapyramidal signs and symptoms were assessed using the Simpson-Angus Rating Scale (SAS) for parkinsonism, Abnormal Involuntary Movement Scale (AIMS) for tardive dyskinesia, and Barnes Akathisia Rating Scale (BARS) for akathisia. All-cause rates of study withdrawal, including for adverse events, were also assessed.

Statistical Analysis

The ITT set consisted of patients who received at least 1 dose of double-blind study medication and had at least 1 follow-up efficacy measurement, while the safety analysis was based on all randomized patients who received at least 1 dose of study medication. The primary endpoint was the change in PANSS total score from baseline to endpoint (i.e., the last postbaseline observation in the double-blind phase). Data analysis used the last-observation-carried-forward approach to impute missing data.

All continuous efficacy data were analyzed using an analysis of covariance model based on the ITT analysis set, including treatment, protocol, and analysis center within protocol (fixed effect) as factors and baseline PANSS total score as covariate. Based on the above model, least squares (LS) estimates, p values, and 95% confidence intervals for the pairwise differences comparing each paliperidone ER treatment group versus placebo were provided. For the analysis comparing rates of treatment response, the responder rate between each paliperidone ER treatment group and placebo was analyzed using the Cochran-Mantel-Haenszel test, controlling for analysis center and protocol. All statistical tests were 2-sided, and no adjustment for multiplicity was made.

RESULTS

Sample Characteristics, Retention, and Treatment

Demographic and clinical characteristics of the pooled sample (N = 1306) at baseline for the ITT population, presented in Table 1, were similar across all groups. Study completion and withdrawal information for all randomized patients is provided in Table 2. Rates of withdrawal for any reason and for lack of efficacy were lower among paliperidone ER–treated patients at all doses relative to placebo ($p < .005$ for all comparisons), while rates of discontinuation due to treatment-emergent adverse events (TEAEs) were similar across all study arms. There were no significant differences between any of the paliperidone ER treatment groups and the olanzapine treatment group in the proportion of study completers or patient withdrawals, regardless of reason. There were also no significant differences in time to discontinuation due to lack of efficacy between any of the paliperidone ER groups and the olanzapine group, while all treatment groups were superior to placebo (Figure 1).

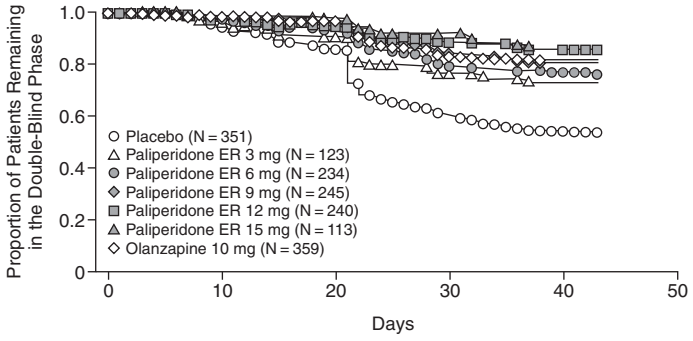
Sixty-four percent of patients in the paliperidone ER treatment groups received supplemental psychotropic medication (antipsychotics and anticonvulsants were ex-

Table 2. Study Completion and Withdrawal Information for All Randomized Patients, N (%)

Status	Placebo (N = 360)	Paliperidone ER 3 mg (N = 127)	Paliperidone ER 6 mg (N = 235)	Paliperidone ER 9 mg (N = 247)	Paliperidone ER 12 mg (N = 242)	Paliperidone ER 15 mg[a] (N = 115)	Paliperidone ER Total (N = 966)	Olanzapine 10 mg (N = 366)
Intent-to-treat	351 (98)	123 (97)	234 (> 99)	245 (99)	240 (99)	113 (98)	955 (99)	359 (98)
Completed	142 (39)	70 (55)	131 (56)	164 (66)	155 (64)	82 (71)	602 (62)	228 (62)
Withdrawn	218 (61)	57 (45)	104 (44)	83 (34)	87 (36)	33 (29)	364 (38)	138 (38)
Lack of efficacy	144 (40)	31 (24)	46 (20)	42 (17)	29 (12)	14 (12)	162 (17)	59 (16)
Subject choice	37 (10)	17 (13)	28 (12)	29 (12)	29 (12)	8 (7)	111 (11)	33 (9)
Adverse event	19 (5)	3 (2)	16 (7)	10 (4)	14 (6)	4 (3)	47 (5)	22 (6)
Lost to follow-up	6 (2)	1 (1)	9 (4)	2 (1)	10 (4)	2 (2)	24 (2)	11 (3)
Study medication noncompliance	3 (1)	1 (1)	0	0	3 (1)	2 (2)	6 (1)	4 (1)
Death	0	0	0	0	0	0	0	1 (< 1)
Other	9 (3)	4 (3)	5 (2)	0	2 (1)	3 (3)	14 (1)	8 (2)

[a]Subjects assigned to 15 mg/day dose group were started on treatment with 12 mg/day during first week of therapy.
Abbreviation: ER = extended-release.

Figure 1. Kaplan-Meier Plot of Time to Discontinuation Due to Lack of Efficacy



Abbreviation: ER = extended-release.

cluded) during the study, compared with 70% in the placebo group. The most commonly used medication was lorazepam (placebo = 54%, paliperidone ER groups = 42% to 59%). The mean ± SD daily dose (mg) of lorazepam was 2.3 ± 1.2 with paliperidone ER and 2.5 ± 1.2 with placebo, while the mean ± SD duration of use was 10.1 ± 8.1 days with paliperidone ER and 9.6 ± 6.4 days with placebo.

Efficacy Results

Psychopathology ratings. Mean PANSS total (Table 3) and subscale factor scores (Table 4) improved significantly from baseline to endpoint across all doses of paliperidone ER compared with placebo ($p \leq .001$). Statistical superiority of paliperidone ER at doses ranging from 3 mg to 15 mg daily compared with placebo was observed both when each of the phase 3 short-term efficacy studies were analyzed individually[15–17] and when the analyses were performed on pooled data from the ITT data set. There were also no relevant differences in mean (SD) change in PANSS total scores between patients randomly assigned to any of the paliperidone ER doses and olanzapine. In general, differences in mean improvement from baseline between paliperidone ER treatment groups and placebo on PANSS total and subscale factors increased with increasing paliperidone ER doses.

Clinical global impressions. Improvement, as measured by changes in clinician-rated CGI-S scores, was significantly greater for all paliperidone ER treatment groups relative to placebo at study endpoint ($p < .001$ for each comparison with placebo) and for every dose within each of the 3 phase 3 studies individually ($p \leq .009$).[15–17] The distribution of the CGI-S scores at endpoint showed that substantially more patients who received paliperidone ER treatment across all doses were classified as "mild," "very mild," or "not ill" compared with those who received placebo (Figure 2). A lower percentage of patients were rated as severe/extremely severe or markedly ill on the CGI-S in the paliperidone ER treatment groups compared with placebo at study endpoint ($p \leq .003$).

Personal and social functioning. Mean ± SD scores on the PSP scale improved at endpoint for all paliperidone ER groups (paliperidone ER 3 mg = 8.3 ± 17.1, 6 mg = 9.0 ± 14.8, 9 mg = 7.8 ± 14.3, 12 mg = 9.5 ± 15.0, 15 mg = 12.2 ± 15.7) versus placebo (0.5 ± 15.0) ($p < .001$) (Table 5). There were no relevant differences in mean change in PSP scores from baseline to endpoint between any of the paliperidone ER treatment groups and the olanzapine treatment group. Differences in LS mean at endpoint for PSP scores between those who received paliperidone ER and placebo were similar across all paliperidone ER doses (Table 5). The proportions of patients with a PSP score of ≥ 71, which corresponds with only mild to no obvious difficulty, increased significantly in each paliperidone ER treatment group and were all (with the exception of the 3 mg group) significantly greater than placebo at study endpoint (Figure 3). At study endpoint, a higher proportion of paliperidone ER–treated patients also demonstrated an improvement of at least 1 category (i.e., one

Table 3. Baseline-to-Endpoint Change in Positive and Negative Syndrome Scale for Schizophrenia[a]

Value	Placebo (N = 351)	Paliperidone ER 3 mg (N = 123)	Paliperidone ER 6 mg (N = 234)	Paliperidone ER 9 mg (N = 245)	Paliperidone ER 12 mg (N = 240)	Paliperidone ER 15 mg (N = 113)	Olanzapine 10 mg (N = 359)
N	351	123	233	245	240	112	359
Baseline score, mean (SD)	93.9 (11.68)	91.6 (12.19)	93.4 (11.22)	93.6 (12.55)	94.4 (11.16)	92.4 (12.36)	93.7 (11.75)
Change, mean (SD)	–4.8 (21.95)	–15.0 (19.61)	–16.9 (20.70)	–16.8 (21.00)	–20.6 (20.15)	–19.9 (18.41)	–18.8 (19.67)
Difference vs placebo							
LS mean (SE)		–11.1 (2.27)	–11.0 (1.70)	–11.8 (1.65)	–14.5 (1.69)	–16.6 (2.34)	
95% CI		–15.61 to –6.68	–14.31 to –7.63	–15.00 to –8.54	–17.82 to –11.18	–21.23 to –12.06	
p Value[b,c]		< .001	< .001	< .001	< .001	< .001	

[a]Negative change in score indicates improvement. Intent-to-treat population.
[b]Based on analysis of covariance model with protocol, treatment (placebo, paliperidone ER 3 mg, 6 mg, 9 mg, 12 mg, 15 mg), and analysis center within protocol as factors and baseline value as a covariate.
[c]Comparisons with placebo without multiplicity adjustment.
Abbreviations: ER = extended-release, LS = least squares.

Table 4. Baseline-to-Endpoint Change in Positive and Negative Syndrome Scale (PANSS) Factor Scores[a]

PANSS Factor	Placebo (N = 351)	Paliperidone ER 3 mg (N = 123)	Paliperidone ER 6 mg (N = 234)	Paliperidone ER 9 mg (N = 245)	Paliperidone ER 12 mg (N = 240)	Paliperidone ER 15 mg (N = 113)	Olanzapine 10 mg (N = 359)
Positive symptoms							
Baseline score, mean (SD)	27.8 (4.54)	27.4 (4.92)	27.7 (4.88)	27.9 (5.15)	27.6 (4.80)	27.6 (5.08)	27.7 (4.82)
Change, mean (SD)	–2.3 (6.97)	–5.0 (6.89)	–5.9 (6.78)	–6.1 (7.30)	–7.2 (6.74)	–6.9 (6.87)	–6.2 (6.45)
p Value (vs placebo)[b,c]		< .001	< .001	< .001	< .001	< .001	
Negative symptoms							
Baseline score, mean (SD)	23.0 (5.18)	22.4 (5.73)	23.1 (5.35)	23.2 (5.08)	23.6 (5.41)	23.0 (5.56)	23.5 (5.69)
Change, mean (SD)	–1.3 (5.98)	–3.8 (5.27)	–4.3 (6.01)	–3.7 (5.39)	–4.5 (5.80)	–4.2 (5.30)	–4.6 (5.83)
p Value (vs placebo)[b,c]		< .001	< .001	< .001	< .001	< .001	
Disorganized thoughts							
Baseline score, mean (SD)	22.0 (4.38)	21.4 (4.29)	21.2 (4.13)	21.9 (4.57)	21.7 (4.25)	21.3 (4.75)	21.7 (4.14)
Change, mean (SD)	–0.9 (5.43)	–3.4 (5.06)	–3.1 (4.74)	–3.2 (5.11)	–4.2 (5.08)	–3.9 (4.46)	–4.0 (4.58)
p Value (vs placebo)[b,c]		< .001	< .001	< .001	< .001	< .001	
Uncontrolled hostility/excitement							
Baseline score, mean (SD)	9.4 (2.88)	9.5 (2.99)	9.7 (3.43)	9.4 (3.19)	9.7 (3.30)	9.4 (2.98)	9.5 (3.23)
Change, mean (SD)	0.7 (4.39)	–1.1 (3.61)	–1.3 (4.11)	–1.5 (4.17)	–2.0 (3.69)	–2.3 (3.34)	1.5 (3.56)
p Value (vs placebo)[b,c]		< .001	< .001	< .001	< .001	< .001	
Anxiety/depression							
Baseline score, mean (SD)	11.7 (3.30)	10.9 (3.53)	11.6 (2.89)	11.2 (2.99)	11.8 (3.34)	11.0 (3.24)	11.3 (3.13)
Change, mean (SD)	–0.9 (3.93)	–1.8 (3.35)	–2.2 (3.47)	–2.3 (3.59)	–2.8 (3.56)	–2.6 (2.87)	–2.6 (3.54)
p Value (vs placebo)[b,c]		< .001	< .001	< .001	< .001	< .001	

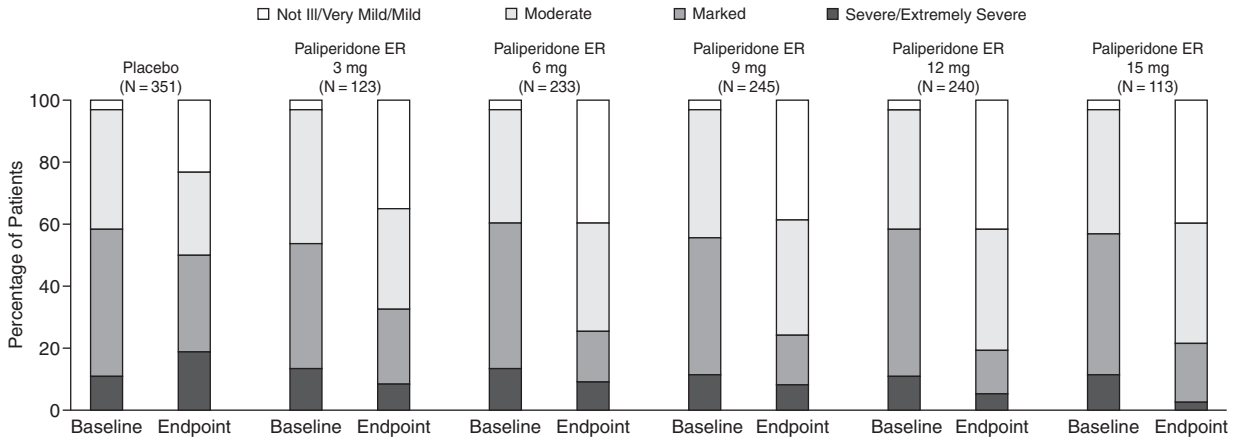
[a]Negative change in score indicates improvement, and factor scores are based on Marder criteria. Positive symptoms: range, 8–56; negative symptoms: range, 7–49; disorganized thoughts: range, 7–49; uncontrolled hostility/excitement: range, 4–28; and anxiety/depression: range, 4–28. Intent-to-treat population.
[b]Based on analysis of covariance model with protocol, treatment (placebo, paliperidone ER 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg), and analysis center within protocol as factors and baseline value as covariate.
[c]Comparisons with placebo without multiplicity adjustment.
Abbreviation: ER = extended-release.

10-point interval) compared with those who received placebo (Figure 4).

Rates of treatment response. A significantly greater proportion of patients in the paliperidone ER treatment groups satisfied a priori symptom-based treatment response criteria by study endpoint (paliperidone ER 3 mg = 39.8%, 6 mg = 53.2%, 9 mg = 48.2%, 12 mg = 56.7%, 15 mg = 52.7%) relative to placebo (27.4%) ($p \leq .001$). Greater differences in response rates were observed for paliperidone ER–treated patients beginning at a dose of 6 mg daily.

Dose-response relationship. The size of the pooled dataset permitted an analysis of dose response for efficacy. There was evidence of modestly enhanced efficacy of paliperidone ER at higher doses (e.g., 12 mg and 15 mg daily), with the smallest effect for the 3-mg dose (Tables 3 and 4). Pairwise comparisons between paliperidone ER dose groups for changes from baseline to endpoint in PANSS total scores indicated that the largest LS mean difference was between the 3 mg group and either the 12 mg or 15 mg paliperidone ER treatment groups (approximately –5.5), followed by smaller LS mean differences ranging from –3.3 to –4.6 that were observed between the 6 mg or 9 mg groups and either the 12 mg or 15 mg groups. Other pairwise differences were small (e.g., ± 1.0 or less), indicating little difference in LS mean differences

Figure 2. Distribution of Patients on the Clinical Global Impressions-Severity of Illness Scale (CGI-S) at Baseline and Endpoint[a]



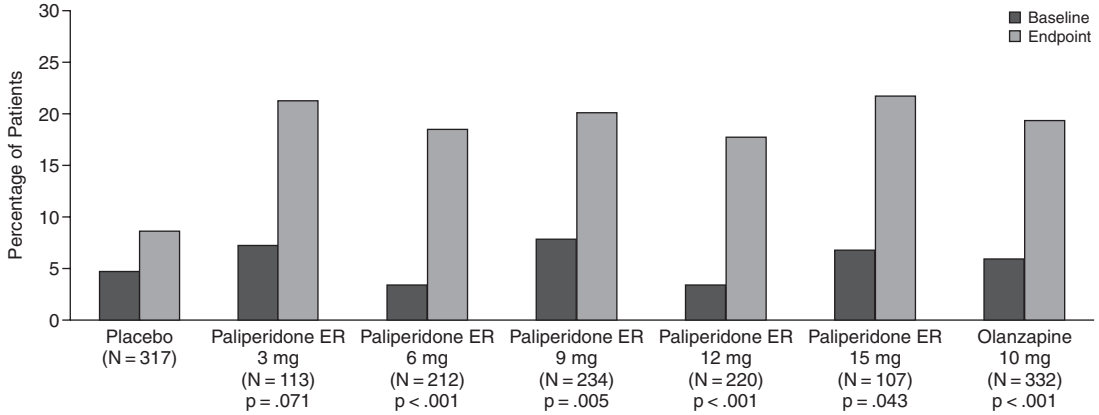
[a]Ns reflect the numbers of patients in the intent-to-treat analysis set for whom CGI-S data were available at baseline and study endpoint.
Abbreviation: ER = extended-release.

Table 5. Baseline-to-Endpoint Changes in Personal and Social Performance Scale Scores[a]

		Paliperidone ER					Olanzapine
Value	Placebo (N = 351)	3 mg (N = 123)	6 mg (N = 234)	9 mg (N = 245)	12 mg (N = 240)	15 mg (N = 113)	10 mg (N = 359)
N	317	113	212	234	220	107	332
Baseline score, mean (SD)	48.1 (13.79)	48.4 (13.72)	46.8 (13.60)	49.0 (15.18)	46.0 (13.71)	47.9 (14.84)	47.5 (14.25)
Change, mean (SD)	0.5 (15.03)	8.3 (17.11)	9.0 (14.81)	7.8 (14.30)	9.5 (15.01)	12.2 (15.65)	8.7 (14.63)
Difference vs placebo							
LS mean (SE)		7.7 (1.67)	7.7 (1.26)	7.3 (1.20)	7.8 (1.25)	11.4 (1.70)	
95% CI		4.39 to 10.96	5.19 to 10.14	4.94 to 9.65	5.35 to 10.27	8.04 to 14.70	
p Value[b,c]		< .001	< .001	< .001	< .001	< .001	

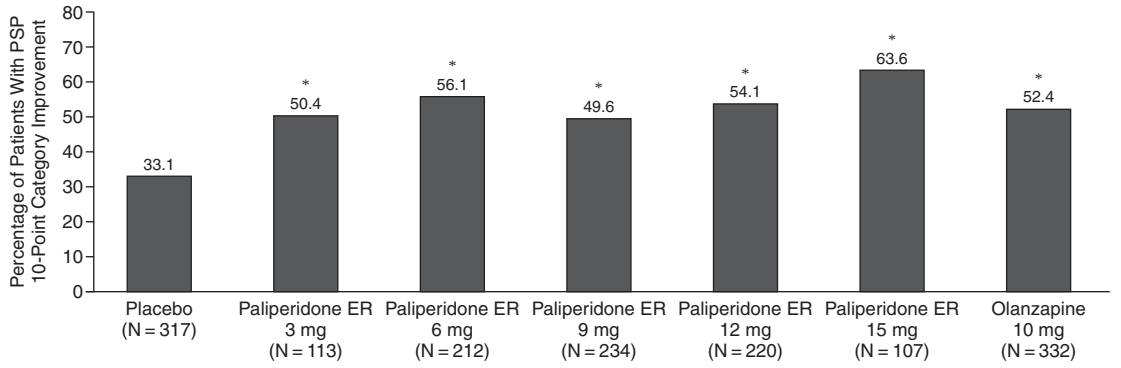
[a]Positive change in score indicates improvement. Intent-to-treat population.
[b]Based on analysis of covariance model with protocol, treatment (placebo and paliperidone ER 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg), and analysis center within protocol as factors and baseline value as a covariate.
[c]Comparisons with placebo without multiplicity adjustment.
Abbreviations: ER = extended-release, LS = least squares.

Figure 3. Proportion of Subjects With a Personal and Social Performance (PSP) Scale Score of ≥ 71 at Baseline and Endpoint[a]



[a]Ns reflect the numbers of patients in the intent-to-treat analysis set for whom PSP scale data were available at baseline and study endpoint. p Values (nominal) are from Cochran-Mantel-Haenszel test comparing each active dose group (paliperidone or olanzapine) with placebo for PSP scale score at endpoint of ≥ 71, controlling for protocol and analysis center. No adjustment for multiplicity was made.
Abbreviation: ER = extended-release.

Figure 4. Proportion of Subjects Achieving ≥ 1 Personal and Social Performance (PSP) Scale 10-Point Category Improvement From Baseline to Endpoint[a]



[a]Ns reflect the numbers of patients in the intent-to-treat analysis set for whom PSP scale data were available at baseline and study endpoint. p Values are based on the Cochran-Mantel-Haenszel test comparing each active dose (paliperidone or olanzapine) with placebo for PSP scale 10-point category improvement from baseline controlling for protocol and analysis center, with no adjustment for multiplicity.
*p < .005 compared with placebo.
Abbreviation: ER = extended-release.

between the 6 mg and 9 mg groups, or between the 12 mg and 15 mg groups.

While all paliperidone ER dose groups were associated with a smaller proportion of patients who discontinued the study due to lack of efficacy compared with the placebo group, the highest proportion of paliperidone ER–treated patients who discontinued treatment for this reason was observed in the 3 mg dosage group. The lowest proportion of paliperidone ER–treated patients who discontinued treatment for lack of efficacy was observed in the 12 mg and 15 mg treatment groups. The 3 mg group was also associated with the lowest rates of symptom-based response rate among all paliperidone ER treatment groups, although the 3-mg dose was statistically superior to placebo for this outcome measure.

Results of a subgroup analysis using the ITT pooled dataset indicated that the efficacy of paliperidone ER was consistent across various demographic subgroups defined by age, race, gender, or geographic region.

Safety and Tolerability Results

The analysis set for adverse events and safety consisted of pooled data from 1682 patients who were randomized and received at least 1 dose of study medication during the 3 phase 3 double-blind studies. The dataset consisted of patients who received paliperidone ER (N = 963), olanzapine (N = 364), or placebo (N = 355). Patients who were randomly assigned to the 15-mg daily dose of paliperidone ER were started on 12 mg per day of paliperidone ER for the first week of treatment. The median duration of double-blind treatment for patients treated with paliperidone ER was 42 days, compared with 28 days for the placebo group.

Treatment-emergent adverse events. The rates of TEAEs for the paliperidone ER, olanzapine, and placebo groups were 66%–77%, 69%, and 66%, respectively (Table 6). Only TEAEs that occurred in ≥ 5% of patients in any treatment group are reported in Table 6. The most common TEAEs were headache and sleep disturbance (insomnia). The rate of discontinuation due to adverse events was comparably low (2%–7%) across all groups (Table 2).

Serious adverse events. Serious adverse events, defined as any event that was life threatening, resulted in hospitalization, or was judged by the investigator as requiring intervention to prevent one of these outcomes, occurred in 6% of patients in the placebo and olanzapine groups and in 5% to 6% of patients in the paliperidone ER treatment groups. Serious adverse events were reported if they occurred at any time during the study or within 30 days after administration of the last dose of study medication. Psychotic disorder and schizophrenia were the most commonly reported serious adverse events. Most of these events, as well as other serious psychiatric disorders, occurred in patients who were hospitalized due to exacerbation of psychotic symptoms. Serious adverse events as categorized by organ class, except psychiatric disorders, were each reported at an incidence not exceeding 1% in any of the treatment groups. There was also no clinically relevant relationship between paliperidone ER dosage and the incidence of serious adverse events. No deaths occurred among any of the patients treated with paliperidone ER in any of the studies. There was no report of neuroleptic malignant syndrome in any of the 3 studies. There were also no reports of esophageal or intestinal obstructive symptoms in patients who received paliperidone ER in any of the phase 3 studies, even though the osmotic-release oral system (OROS) tablet is nondeformable.

Table 6. Treatment-Emergent Adverse Events With ≥ 5% Incidence in Any Treatment Group, N (%)[a]

Body System or Organ Class (MedDRA term)	Placebo (N = 355)	Paliperidone ER 3 mg (N = 127)	Paliperidone ER 6 mg (N = 235)	Paliperidone ER 9 mg (N = 246)	Paliperidone ER 12 mg (N = 242)	Paliperidone ER 15 mg (N = 113)	Paliperidone ER Total (N = 963)	Olanzapine 10 mg (N = 364)
Total no. of patients with adverse events	235 (66)	91 (72)	156 (66)	171 (70)	184 (76)	87 (77)	689 (72)	252 (69)
Nervous system disorders	97 (27)	34 (27)	68 (29)	99 (40)	110 (45)	47 (42)	358 (37)	123 (34)
Headache	42 (12)	14 (11)	29 (12)	34 (14)	35 (14)	20 (18)	132 (14)	35 (10)
Akathisia	14 (4)	5 (4)	7 (3)	20 (8)	23 (10)	11 (10)	66 (7)	7 (2)
Extrapyramidal disorder	8 (2)	6 (5)	5 (2)	17 (7)	18 (7)	9 (8)	55 (6)	6 (2)
Somnolence	12 (3)	6 (5)	8 (3)	17 (7)	11 (5)	7 (6)	49 (5)	47 (13)
Dizziness	14 (4)	7 (6)	11 (5)	11 (4)	12 (5)	7 (6)	48 (5)	19 (5)
Sedation	13 (4)	1 (1)	12 (5)	8 (3)	15 (6)	2 (2)	38 (4)	24 (7)
Psychiatric disorders	111 (31)	33 (26)	59 (25)	61 (25)	57 (24)	33 (29)	243 (25)	96 (26)
Insomnia	51 (14)	14 (11)	29 (12)	35 (14)	26 (11)	14 (12)	118 (12)	42 (12)
Anxiety	29 (8)	12 (9)	16 (7)	14 (6)	11 (5)	9 (8)	62 (6)	21 (6)
Agitation	28 (8)	7 (6)	17 (7)	13 (5)	13 (5)	3 (3)	53 (6)	25 (7)
Psychotic disorder	16 (5)	5 (4)	6 (3)	7 (3)	4 (2)	4 (4)	26 (3)	12 (3)
Gastrointestinal disorders	58 (16)	25 (20)	47 (20)	44 (18)	62 (26)	28 (25)	206 (21)	62 (17)
Nausea	19 (5)	8 (6)	9 (4)	10 (4)	10 (4)	2 (2)	39 (4)	8 (2)
Vomiting	17 (5)	2 (2)	6 (3)	9 (4)	12 (5)	8 (7)	37 (4)	5 (1)
Constipation	20 (6)	7 (6)	8 (3)	7 (3)	7 (3)	4 (4)	33 (3)	14 (4)
Dyspepsia	14 (4)	3 (2)	6 (3)	5 (2)	12 (5)	6 (5)	32 (3)	13 (4)
Cardiac disorders	43 (12)	22 (17)	37 (16)	45 (18)	41 (17)	15 (13)	160 (17)	52 (14)
Tachycardia	10 (3)	3 (2)	17 (7)	18 (7)	18 (7)	2 (2)	58 (6)	13 (4)
Sinus tachycardia	15 (4)	11 (9)	9 (4)	10 (4)	17 (7)	8 (7)	55 (6)	20 (5)
Investigations	42 (12)	22 (17)	31 (13)	32 (13)	34 (14)	18 (16)	137 (14)	75 (21)
Electrocardiogram QTc prolonged	9 (3)	4 (3)	9 (4)	7 (3)	12 (5)	4 (4)	36 (4)	10 (3)

[a]Safety analysis dataset consisted of 1682 adult patients with schizophrenia who received at least 1 dose of double-blind study medication during the phase 3 double-blind studies.
Abbreviation: ER = extended-release.

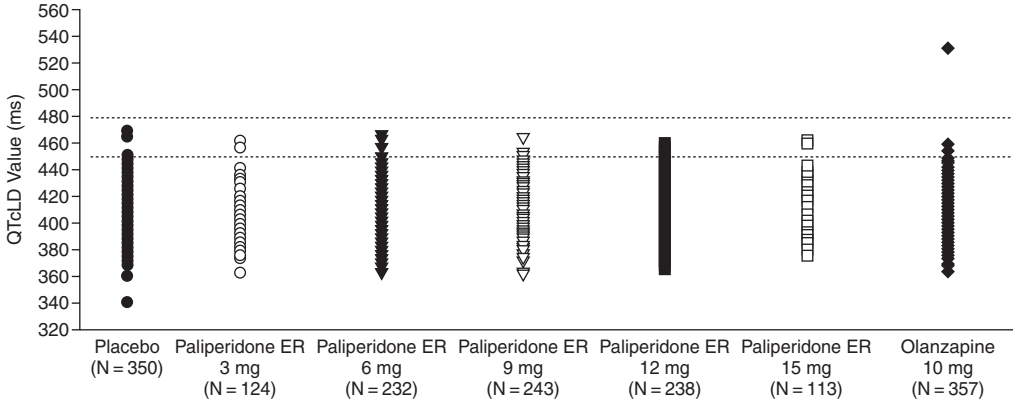
Ten patients who were randomly assigned to paliperidone ER treatment (1%) and 5 patients who received placebo (1%) reported a suicidality-related adverse event (defined as suicidal ideation or an attempt of sufficient significance to be reported by the investigator as an adverse event). An estimate based on patient-years of exposure indicated that the rate of suicidality-related adverse events was greater for placebo-treated patients than for those who received paliperidone ER. The rates of suicidal ideation and suicide attempts per patient-years of exposure for the placebo group were 14.5 and 3.6, respectively, compared with 10.3 and 1.1 for the paliperidone ER groups.

Cardiovascular safety. The most common cardiovascular-related TEAEs included tachycardia and sinus tachycardia (Table 6). In the pooled analysis, there were no clinically relevant differences in TEAEs suggestive of proarrhythmic potential between placebo or any paliperidone ER treatment groups. Syncope was reported in a low percentage of patients who received paliperidone ER (N = 8, 0.8%) or placebo (N = 1, 0.3%). No adverse events of sudden death, ventricular fibrillation or flutter, or torsades de pointes occurred among patients who received paliperidone ER.

In the phase 3 studies, orthostatic changes were assessed by monitoring patients for adverse events related to orthostatic hypotension. The incidence of orthostatic hypotension reported as a TEAE for paliperidone ER doses of 3 mg (2%), 6 mg (1%), and 9 mg (2%) was similar to that of placebo (1%). Higher incidence rates were reported among those who received paliperidone ER doses of 12 mg (4%) and 15 mg (3%). Orthostatic hypotension was not reported as a serious or treatment-limiting adverse event in any patient treated with paliperidone ER.

In each of the phase 3 studies, 12-lead ECGs were obtained for all patients at screening, baseline, each specified study visit (days 4, 8, 15, 29, 36, and 43), and a post-study visit (day 50). Care was taken to record ECGs at approximately the same time of day, including times corresponding to maximum plasma concentration (C_{max}) values. In the pooled analysis, LS mean differences in linear-derived QTc (QTcLD) between placebo and all paliperidone ER treatment groups were small (< 4 ms). None of the 1300 patients receiving paliperidone ER or placebo in the phase 3 studies and who had ECG data available had a QTcLD of 480 ms or higher at any time during the double-blind treatment period (Figure 5). There were no clinically relevant differences between the proportions of patients who had a normal QTc on electrocardiography (< 450 ms) at baseline and a maximum post-baseline QTc value of ≥ 450 ms and < 480 ms among

Figure 5. Scatterplot of Maximum Postbaseline Linear-Derived QTc (QTcLD) Values[a]



[a]Safety analysis set. Dashed horizontal lines represent the QTc limit classifications in accordance with the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use E14 Guideline for abnormal corrected QT intervals: < 450 ms = normal, ≥ 450 to < 480 ms = borderline, ≥ 480 ms = prolonged.
Abbreviation: ER = extended-release.

Table 7. Treatment-Emergent Extrapyramidal Symptom (EPS)–Related Adverse Events, N (%)[a]

		Paliperidone ER					Olanzapine
EPS Group[b] (MedDRA term)	Placebo (N = 355)	3 mg (N = 127)	6 mg (N = 235)	9 mg (N = 246)	12 mg (N = 242)	15 mg (N = 113)	10 mg (N = 364)
Total no. of patients with any EPS-related adverse event	39 (11)	16 (13)	24 (10)	62 (25)	63 (26)	27 (24)	31 (9)
Dyskinesia[c]	12 (3)	6 (5)	6 (3)	19 (8)	21 (9)	10 (9)	7 (2)
Dyskinesia	3 (1)	0	1 (< 1)	1 (< 1)	4 (2)	1 (1)	1 (< 1)
Extrapyramidal disorder	8 (2)	6 (5)	5 (2)	17 (7)	18 (7)	9 (8)	6 (2)
Dystonia[c]	4 (1)	1 (1)	3 (1)	13 (5)	11 (5)	2 (2)	3 (1)
Dystonia	2 (1)	1 (1)	3 (1)	9 (4)	9 (4)	1 (1)	1 (< 1)
Muscle spasms	1 (< 1)	0	0	1 (< 1)	2 (1)	1 (1)	1 (< 1)
Oculogyration	0	0	0	5 (2)	0	0	0
Hyperkinesia[c]	14 (4)	5 (4)	7 (3)	20 (8)	24 (10)	11 (10)	8 (2)
Akathisia	14 (4)	5 (4)	7 (3)	20 (8)	23 (10)	11 (10)	7 (2)
Parkinsonism[c]	8 (2)	4 (3)	6 (3)	18 (7)	15 (6)	7 (6)	8 (2)
Drooling	1 (< 1)	0	2 (1)	1 (< 1)	0	2 (2)	1 (< 1)
Hypertonia	4 (1)	3 (2)	3 (1)	10 (4)	8 (3)	4 (4)	5 (1)
Muscle rigidity	0	1 (1)	0	3 (1)	1 (< 1)	0	0
Parkinsonism	0	0	1 (< 1)	5 (2)	3 (1)	2 (2)	2 (1)
Tremor	12 (3)	4 (3)	6 (3)	11 (4)	8 (3)	3 (3)	8 (2)

[a]Safety analysis data set consisted of 1682 adult patients with schizophrenia who received at least 1 dose of double-blind study medication during the phase 3 double-blind studies.
[b]Only EPS-related adverse events reported in at least 5 (0.5%) of the total patients receiving paliperidone ER are shown in this table.
[c]Dyskinesia includes MedDRA preferred terms of *dyskinesia, extrapyramidal disorder, muscle twitching, tardive dyskinesia.* Dystonia includes MedDRA preferred terms of *dystonia, muscle spasms, oculogyration, trismus*. Hyperkinesia includes MedDRA preferred terms of *akathisia, hyperkinesia, restless legs syndrome*. Parkinsonism includes MedDRA preferred terms of *bradykinesia, cogwheel rigidity, drooling, hypertonia, hypokinesia, muscle rigidity, musculoskeletal stiffness, parkinsonism.*
Abbreviation: ER = extended-release.

patients treated with paliperidone ER (1.6%) and placebo (1.4%).

Extrapyramidal symptom–related adverse events. Extrapyramidal symptom (EPS)–related adverse events were reported in all treatment groups (Table 7). There were no clinically relevant differences in median changes from baseline to endpoint in BARS, AIMS total, and SAS global scores between placebo and any of the paliperidone ER treatment groups. Most patients showed no change in the SAS global scores, indicating that the majority of patients did not experience any change in the severity of these symptoms. However, of those paliperidone ER–treated patients who did evidence an increase in SAS, a higher proportion were randomly assigned to paliperidone ER doses that exceeded 6 mg/day. In addition, a higher proportion of patients who received doses of paliperidone ER above 6 mg/day experienced EPS-related adverse events (e.g., dystonia, dyskinesia, parkinsonism,

Table 8. Prolactin Concentration at Baseline and Endpoint Among Female and Male Patients

	Female Patients			Male Patients		
Group	N	Prolactin (ng/mL), Mean ± SD	Prolactin (ng/mL), Median (range)	N	Prolactin (ng/mL), Mean ± SD	Prolactin (ng/mL), Median (range)
Placebo						
Baseline	116	34.3 ± 46.9	15.7 (3–257)	215	13.3 ± 11.4	9.8 (1–60)
Endpoint	116	20.8 ± 22.0	14.0 (3–134)	215	12.5 ± 14.4	8.5 (1–161)
Paliperidone ER 3 mg						
Baseline	44	53.6 ± 90.9	20.2 (3–446)	76	14.1 ± 12.3	10.9 (1–67)
Endpoint	44	115.7 ± 121.2	78.2 (6–750)	76	29.5 ± 15.6	27.5 (5–79)
Paliperidone ER 6 mg						
Baseline	93	32.3 ± 49.0	17.9 (2–382)	124	15.1 ± 13.9	9.8 (1–65)
Endpoint	93	105.2 ± 71.8	88.1 (9–365)	124	39.5 ± 29.1	33.2 (3–177)
Paliperidone ER 9 mg						
Baseline	91	37.3 ± 63.6	13.8 (3–426)	143	17.6 ± 20.1	9.4 (1–118)
Endpoint	91	125.0 ± 65.8	127.2 (11–297)	143	45.3 ± 25.4	43.3 (3–141)
Paliperidone ER 12 mg						
Baseline	90	31.7 ± 44.3	15.5 (4–262)	141	17.1 ± 22.2	9.7 (2–150)
Endpoint	90	127.9 ± 68.8	114.4 (5–345)	141	44.4 ± 24.4	41.7 (2–169)
Paliperidone ER 15 mg						
Baseline	40	23.2 ± 27.4	14.1 (5–136)	70	17.5 ± 18.2	11.0 (1–90)
Endpoint	40	130.1 ± 63.1	118.5 (10–287)	70	52.8 ± 38.2	44.9 (6–247)

Abbreviation: ER = extended-release.

and hyperkinesia). There were no clinically relevant differences in the incidence of EPS-related adverse events between olanzapine and placebo. Across all 3 studies, only 1 patient was reported to have tardive dyskinesia. The patient was a 54-year-old woman with a history of tardive dyskinesia and clozapine use who experienced the "emergence of tardive dyskinesia" on day 4 of double-blind treatment with paliperidone ER 9 mg/day. A causal relationship between paliperidone ER and the patient's tardive dyskinesia symptoms could not be determined due to her prior history of tardive dyskinesia, her recent withdrawal from prior antipsychotic medication, and the emergence of symptoms soon after the initiation of double-blind treatment.

Markers of glucose homeostasis and lipid metabolism. Mean changes from baseline to endpoint in serum glucose were small (0.1 mmol/L) for the pooled paliperidone ER–treated group, and were similar to placebo, in all phase 3 studies. Potentially glucose-related adverse events were reported in 1% (N = 8) of patients in the paliperidone ER groups and 1% of patients in the placebo group (N = 2). The most common event was an increase in blood glucose levels (paliperidone ER groups, N = 4; placebo group, N = 1). Two glucose-related adverse events in patients treated with paliperidone ER were considered serious. One event (blood glucose increase) occurred in a patient with no prior history of diabetes who was treated with paliperidone ER 15 mg/day. This patient was withdrawn from the study as a result of this adverse event, which resolved after treatment discontinuation.

Mean changes in serum levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides from baseline to endpoint among paliperidone ER–treated patients were small (≤ 0.1 mmol/L). These changes were not considered clinically significant.

Changes in body weight. Mean ± SD changes in body weight (kg) at study endpoint were < 2 kg in all paliperidone treatment groups: 3 mg = 0.6 ± 2.8; 6 mg = 0.6 ± 3.2, 9 mg = 1.0 ± 3.0, 12 mg = 1.1 ± 3.1, and 15 mg = 1.9 ± 3.6, compared with placebo (–0.4 ± 3.5). While the weight gain appeared to be dose related, the overall increase was small within the recommended dose range of 3 mg to 12 mg. The mean ± SD change in body weight (kg) at study endpoint in the olanzapine group was 2.0 ± 3.7.

Prolactin-related adverse events. Consistent with its pharmacologic profile as a dopamine D_2-receptor antagonist, paliperidone ER was associated with elevations in serum prolactin levels. Absolute changes in prolactin levels by gender among patients in the combined dataset are reported in Table 8. Median increases in prolactin concentration were larger among female patients (81 ng/mL) than male patients (24 ng/mL) when all paliperidone ER doses were combined. The magnitude of median increases in prolactin concentration related to paliperidone ER treatment increased with increasing doses. Maximum median increases in prolactin concentrations were generally observed on day 15 and decreased slightly thereafter; however, prolactin levels remained elevated above the upper limit of the reference range (1.39–24.20 ng/mL for females; 1.61–18.77 ng/mL for males). Spontaneously reported potentially prolactin-related adverse events (e.g., impotence or other sexual dysfunction, galactorrhea, gynecomastia, amenorrhea, or menstrual irregularity) were reported among 1% to 2% of patients who received placebo or paliperidone ER at doses of 3 mg to 12 mg but did not result in discontinuation of treatment. There were

no potentially prolactin-related adverse event terms that applied to more than 1 subject in any treatment group. Potentially prolactin-related adverse events were reported by 4% of patients who received paliperidone ER at 15 mg.

DISCUSSION

The main objective of this pooled analysis was to conduct a benefit versus risk analysis of paliperidone ER over a daily dosage range of 3 mg to 15 mg. The results of this pooled analysis demonstrated that all doses of paliperidone ER (3, 6, 9, 12, and 15 mg) given once daily for 6 weeks were efficacious in the treatment of an acute episode of schizophrenia. All paliperidone ER doses were superior to placebo across all efficacy variables, including psychiatric symptomatology/psychopathology and personal and social functioning. Changes from baseline to endpoint in PANSS total and subscale scores, rates of study dropout regardless of cause, and the proportion of patients who satisfied a priori response criteria were similar between all paliperidone ER groups and olanzapine and were superior to placebo. After 6 weeks of treatment with paliperidone ER, approximately 50% of patients achieved a clinically significant response rate of at least 30% improvement in the PANSS total score, while about 40% of patients were rated clinically as "not ill" or as having only very mild or mild disease severity.

The pooled analysis also indicated that paliperidone ER was both effective and very well tolerated during acute phase treatment, as evidenced by the low discontinuation rates for all causes, inefficacy, and intolerability. The overall adverse effect burden of paliperidone ER appeared to be low. At lower doses, the profiles for EPS signs and symptoms and potentially prolactin-related symptoms were similar to placebo, while higher doses (≥ 9 mg) of paliperidone ER were associated with higher rates of EPS effects. At higher doses, median scores of 0 on the 3 EPS rating scales at baseline and endpoint indicated no significant change in these symptoms during the course of acute treatment. No paliperidone ER treatment groups were associated with clinically significant mean increases in body weight, glycemic measures, or serum lipids over 6 weeks of treatment.

In recent years, there has been an increasing emphasis on measuring clinical outcomes beyond changes in symptomatology that are relevant to patients with schizophrenia and their caregivers. These include the ability to function socially, vocationally, and in the community, all of which are now considered to be fundamental treatment goals. For each of the 3 phase 3 studies, the PSP scale, a schizophrenia-specific instrument, was used to provide complementary data concerning social functioning of patients. In all 3 double-blind studies, paliperidone ER treatment was associated with statistically significant and clinically relevant (≥ 10-point) increases in PSP total scores at study endpoint, relative to placebo. Approximately 20% of patients who received paliperidone ER had a PSP score indicative of none to only mild impairment (≥ 71) after 6 weeks of treatment. Performance on these outcome measures of paliperidone ER was similar to that of olanzapine 10 mg/day.

The clinical efficacy data for paliperidone ER reported in this analysis are similar to those reported for oral risperidone during acute phase schizophrenia treatment trials (see Hunter et al.[20]). Rates of treatment-emergent EPS signs and symptoms observed in the paliperidone ER groups, even at higher doses, were lower than those observed for risperidone during acute, short-term studies.[20,21] In addition, only a very low incidence of signs and symptoms potentially related to prolactin elevations was observed, although mean changes in prolactin concentrations were similar to those of risperidone.[22] It is difficult to make direct comparisons between risperidone and paliperidone ER in terms of either efficacy or side effect burden, since none of these studies allowed direct comparisons between the 2 drugs. Because risperidone is converted to paliperidone via oxidation by hepatic CYP2D6, and because polymorphisms resulting in an inactive CYP2D6 phenotype occur in < 10% of Caucasians and are even rarer in other ethnic groups,[23–25] it may be argued that such a comparison would be unnecessary for a majority of patients.

Both risperidone and paliperidone bind with higher and similar nanomolar affinity to 5-HT_{2A} receptors than they do to D_2 receptors, as indicated by their respective ratios of the inverse of their K_i values at 5-HT_{2A} and D_2 receptors ($1/K_i$ for 5-HT_{2A}/ $1/K_i$ for D_2) using the data from Schotte et al.[10]: 36.9 for paliperidone and 19.2 for risperidone. Taken together, such a profile may predict a low EPS and hyperprolactinemic burden for paliperidone relative to risperidone. This position awaits prospective investigation. Plasma concentrations of risperidone and 9-OH-risperidone show large interindividual variability even among extensive CYP2D6 metabolizers[26]; therefore, the incidence of antidopaminergic adverse effects could still differ between risperidone and paliperidone.

Significant improvements in mean PANSS total scores for all paliperidone ER doses were evident at every post-baseline timepoint in all studies, including from day 4, a property that would be most desirable for use in acute treatment. This result is consistent with those from a multicenter, double-blind, placebo-controlled study of 311 patients with an acute exacerbation of schizophrenia and related diagnoses who were randomly assigned to receive intramuscular injections of 10 mg of olanzapine, 7.5 mg of haloperidol, or placebo.[27] Significant decreases in PANSS items that reflected improvements in core psychotic symptoms such as conceptual disorganization, hallucinosis, and unusual thought content were observed within 24 hours of initiating treatment and were not medi-

ated by nonspecific effects on behavior or other psychopathologic domains. In the paliperidone ER studies, differences from baseline in PANSS total scores continued to widen for most doses as the studies progressed, consistent with a report by Emsley et al.[28] that documented a wide variety of time intervals required for a therapeutic response among risperidone- and haloperidol-treated patients with acute first-break schizophrenia. In that study, 22.5% of the sample achieved a therapeutic response after week 4, while an additional 11.2% required 8 weeks.

This pooled data analysis allowed for examination of a very large sample of patients included in the ITT analysis and randomly assigned to active treatment (N = 955) at multiple fixed doses or placebo (N = 351). The studies were identical in design, duration, and outcome measures and yielded very consistent results for both measures of clinical efficacy and safety/tolerability. All 3 studies also included an active control group, which consisted of patients who received fixed doses of olanzapine (10 mg/day) for assay sensitivity. As previously mentioned, although the individual phase 3 studies were not designed to detect differences in efficacy or safety/tolerability between paliperidone ER at any dose and olanzapine 10 mg/day, the large size of the pooled dataset allowed for some comparison for several outcome measures. The large size of this dataset also allowed a better estimation of the incidence of rarely occurring adverse events, such as dyskinesia and neuroleptic malignant syndrome.

The 3 studies described here were designed to test the short-term acute phase efficacy of paliperidone ER across several fixed doses compared with placebo. Longer-term studies are needed to assess the long-term effectiveness of paliperidone ER as well as its safety profile with continued use, especially for weight gain, metabolic status, and antidopaminergic effect, such as EPS and prolactin-related side effects. The only longer-term placebo-controlled study available to date involving paliperidone ER is a randomized, double-blind, parallel-group study designed to compare rates of recurrence of symptoms of schizophrenia (defined a priori) between flexibly dosed paliperidone ER (3–15 mg/day after a 14-week run-in/stabilization phase) and placebo.[29] Twenty-five percent of patients randomly assigned to placebo versus flexibly dosed paliperidone ER experienced recurrence at 23 days versus 83 days, respectively, during the double-blind phase ($p < .001$). The mean modal dose of paliperidone ER during the double-blind phase was 10.8 mg/day. PANSS total and CGI-S scores decreased significantly from run-in baseline to the end of the double-blind phase. There were no significant differences between placebo and paliperidone ER groups for body weight (kg), body mass index (kg/m^2), or movement disorder scale scores (SAS global, AIMS, BARS global).

Paliperidone ER appears to be a safe, well-tolerated, and effective oral antipsychotic medication for the acute phase treatment of schizophrenia. Our pooled analysis supports the use of paliperidone ER, administered once daily, across all doses studied. The highest dose (15 mg daily) has not been included in the label for paliperidone ER. The 3-mg daily dose was shown to be effective, but less so than the higher doses of paliperidone ER. As there is limited hepatic metabolism of paliperidone ER, the patient's metabolic status is almost never of clinical relevance for dosing.[30]

The efficacy profile was similar over 6 weeks of treatment to that of olanzapine 10 mg daily. The incidence of EPS effects appears to increase with higher doses, beginning at 9 mg daily. Baseline-to-endpoint increases in prolactin levels also appear to be dependent on drug dosage over 6 weeks of treatment. Therefore, 6 mg daily appears to offer a good balance between safety and efficacy and is the recommended starting dose. Future longer-term studies will clarify important clinical issues that require longer periods of time to develop, including selected adverse effects (discussed previously) and aspects of clinical efficacy, such as negative symptoms and cognition.

Drug names: clozapine (FazaClo, Clozaril, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), paliperidone (Invega), risperidone (Risperdal).

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