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Original Article

A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder

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Objectives: To evaluate the antimanic efficacy and safety of paliperidone extended-release (ER) tablets in patients with bipolar I disorder.

Methods: This study included a 3-week, double-blind, acute treatment phase (paliperidone ER versus placebo, with quetiapine as control), and a 9-week, double-blind, maintenance phase (paliperidone ER versus quetiapine). Patients [n = 493; Young Mania Rating Scale (YMRS) score ≥ 20] were randomized (2:2:1) to flexibly dosed paliperidone ER (3–12 mg/day), quetiapine (400–800 mg/day), or placebo for the acute treatment phase. During the maintenance phase, patients assigned to placebo were switched to paliperidone ER but not included in analysis of efficacy.

Results: Paliperidone ER was superior to placebo at the 3-week endpoint {primary outcome; least-squares mean difference in change from baseline in YMRS scores [95% confidence interval (CI)]: −5.5 (−7.57; −3.35); $p < 0.001$} and noninferior to quetiapine at the 12-week endpoint [least-squares mean difference (95% CI): 1.7 (−0.47; 3.96)]. The median mode dose during the 12-week treatment period was 9 mg for paliperidone ER and 600 mg for quetiapine. The most common (≥ 10%) treatment-emergent adverse events during the 12-week period were: headache (16%), somnolence (10%), and akathisia (10%) for paliperidone ER; somnolence (21%), sedation and dry mouth (17% each), headache (14%), and dizziness (13%) for quetiapine. Body weight increase ≥ 7% from baseline to 12-week endpoint was 8% with paliperidone ER and 17% with quetiapine. A higher percentage of paliperidone ER (13.9%) versus quetiapine patients (7.5%) 'switched to depression' at the12-week endpoint.

Conclusions: Paliperidone ER (3–12 mg/day) was efficacious and tolerable in the treatment of acute mania.

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Bipolar disorder is an episodic illness characterized by recurrent manic, mixed, and depressive episodes with an estimated global prevalence of 1–5% (1). The illness is associated with high levels of

mortality and morbidity (2), functional impairment (3), and high rates of suicide (4). Although several options exist for the treatment of acute mania, including lithium and anticonvulsants (4), their efficacy is often limited by their adverse effects and associated poor adherence (5, 6). Hence, optimal treatment for bipolar disorder is still a major unmet need. Recent evidence indicates that atypical antipsychotics, used for many years in the treatment of schizophrenia, are also effective in the treatment of manic symptoms either alone or in combination with traditional mood stabilizers (5, 7).

Paliperidone, an atypical antipsychotic agent, has been approved in the United States, European Union, and many other markets for the acute and maintenance treatment of schizophrenia. Paliperidone extended-release (ER) tablets (3–12 mg) utilize OROS® (Alza Corp., Mountain View, CA, USA) drug delivery technology, which results in stable plasma concentrations over 24 hours (8) that permit once-daily dosing and initiation of treatment with a potentially efficacious dose without the need for titration (9).

Paliperidone ER is predominantly eliminated by renal filtration, resulting in a low potential for drug-drug interactions. Its low affinity for muscarinic receptors results in an absence of anticholinergic adverse effects (10). The efficacy and tolerability of paliperidone ER, as well as its ability to reduce symptom recurrence in patients with schizophrenia, was demonstrated in several randomized, controlled trials (11–14). Tolerability in longer-term open-label trials (up to 52 weeks) has also been shown in patients with schizophrenia (15).

The objectives of this double-blind, parallel-group study were primarily to evaluate the antimanic efficacy and safety of flexibly dosed paliperidone ER tablets (3−12 mg/day) versus placebo over 3 weeks of treatment, and secondarily to assess noninferiority of paliperidone ER versus quetiapine over 12 weeks of treatment, in patients with bipolar I disorder presenting with an acute manic or mixed episode.

Methods

Study population

Men and women, aged 18–65 years (inclusive), with a Diagnostic and Statistical Manual 4th edition (DSM-IV) (16) diagnosis of bipolar I disorder and experiencing acute manic or mixed episodes were enrolled in the study. Patients needed to have at least one documented manic or mixed episode requiring treatment within the three years prior to screening and a Young Mania Rating Scale (YMRS) (17) score of at least 20 at screening and baseline.

Patients were excluded if they met DSM-IV criteria for rapid cycling and schizoaffective disorders and had known or suspected borderline or antisocial personality disorder or a history of substance dependence. Patients with serious medical illnesses, suspected seizure disorders, moderate to severe tardive dyskinesia, history of neuroleptic malignant syndrome, or history of hypersensitivity or intolerance to paliperidone, risperidone, or quetiapine at screening were also excluded from the study.

The independent ethics committee or institutional review board at each study site approved the protocol. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, consistent Good Clinical Practices, and applicable regulatory requirements. All participants or their legal representatives provided written informed consent.

Study design

This randomized, double-blind, placebo-controlled study was conducted from May 2006 to November 2007 at 52 centers across eight countries (Greece, Lithuania, Republic of Korea, Russia, Taiwan, Turkey, Ukraine, and the United States).

The study consisted of: (i) a one-week screening and washout phase, during which patients discontinued their current antimanic, mood-stabilizing treatment or other excluded medications or treatments; (ii) a 3-week double-blind acute treatment phase, during which patients were randomly assigned in a 2:2:1 ratio to receive paliperidone ER (3–12 mg/day, flexibly dosed), quetiapine (400–800 mg/day, initially titrated and flexibly dosed), or placebo; (iii) a 9-week double-blind maintenance phase, during which patients continued with flexible doses of their respective study medication (i.e., either paliperidone ER or quetiapine) received during the 3-week acute treatment phase (patients on placebo were switched, in a blinded fashion, to flexibly dosed paliperidone ER at an initial dose of 6 mg/day); and (iv) a post-treatment follow-up phase for safety evaluations, approximately one week after end-of-study or early-withdrawal assessments. Patients were randomly allocated via an interactive voice-response system and a computer-generated randomization schedule balanced by using permuted blocks of treatments and stratified by center. The study,

including the screening and washout phase, lasted approximately 98 days (14 weeks).

Patients were hospitalized for at least the first seven days during the acute treatment phase. Paliperidone ER was initiated at a dose of 6 mg/day on day 1. Doses could be increased by 3 mg/day to a maximum dose of 12 mg/day, or decreased by the amount the investigator deemed necessary within the dose range of 3–12 mg/day. Quetiapine was initiated at 100 mg/day on day 1, with forced titration to 400 mg/day at day 4, and subsequent dose adjustments in increments of 200 mg/day to a maximum of 800 mg/day (maximum approved daily dosage) (18), or decrements as deemed necessary by the investigator within the dose range of 400–800 mg/day.

Dose adjustments in any group could be made at least two days apart. Patients on paliperidone ER and quetiapine who completed the acute treatment phase continued their treatment during the 9-week maintenance phase, while patients on placebo who completed the acute treatment phase were switched in a blinded manner to paliperidone ER (placebo/paliperidone ER group) with the same initiation dosing schedule for paliperidone ER as used in the acute treatment phase. Patients who had not improved sufficiently [i.e., a Clinical Global Impression-Bipolar Disorder-Severity (CGI-BP-S) (19) score ≤ 3] to be released from the hospital by the end of the acute treatment phase were discontinued from the study and switched to appropriate, alternative medication.

Paliperidone ER 3 mg and paliperidone ER 6 mg were capsule-shaped longitudinal compressed tablets consisting of two drug layers and a push layer with a Push-Pull™ delivery system (proprietary OROS® pump technology, Alza Corp., Mountain View, CA, USA), designed to deliver 3 mg and 6 mg of paliperidone. Quetiapine was provided in 50 mg, 100 mg, and 200 mg capsules, which were prepared from 25 mg and 100 mg quetiapine tablets. All active medication and matching placebo tablets were over-encapsulated. Paliperidone ER was administered once daily and quetiapine twice daily in equally divided doses. To maintain study blind, all treatments were given twice daily, with placebo administered as necessary.

Concomitant medications

Benzodiazepines [lorazepam (up to 8 mg/day), clonazepam (up to 4 mg/day), or diazepam (up to 80 mg/day)] as rescue medication were allowed, when clinically indicated, during the screening and washout phase and up to day 14 of the acute treatment phase (in gradually decreasing doses). Anticholinergics and antihistamines were allowed for the relief of treatment-emergent extrapyramidal symptoms (EPS).

Efficacy assessments

The primary efficacy variable was the change from baseline in YMRS total score at the 3-week endpoint for paliperidone ER versus placebo. The key secondary efficacy variable was the change from baseline in Global Assessment of Functioning (GAF) score (DSM-IV) at the 3-week endpoint for paliperidone ER versus placebo. Other secondary efficacy variables included a noninferiority analysis of paliperidone ER to quetiapine based on change in YMRS score at the 12-week endpoint.

Additional endpoints were change in Positive and Negative Syndrome Scale (PANSS) (20) score, CGI-BP-S score, onset of effect (first time point at which the paliperidone ER group was statistically different from placebo and remained different thereafter until the 3-week endpoint, based on the change from baseline in the YMRS total score), responder rate (percentage of patients with $\geq 50\%$ reduction in YMRS total score), and remission rate (percentage of patients who had YMRS total score ≤ 12) at both the 3- and 12-week endpoints. Patients in the placebo/paliperidone ER group were not included in the 12-week efficacy comparisons.

Both YMRS and CGI-BP-S scores were assessed at baseline, days 1, 2, 4, and 7 of the first week, weekly thereafter up to day 70, and at end-of-study or early withdrawal on day 84 (YMRS was additionally assessed at screening, and CGI-BP-S on day 6 and at post-treatment follow-up). GAF and PANSS scores were assessed at baseline and endpoint of acute treatment and maintenance phases. Change from baseline to the 3-week and 12-week endpoint in sleep visual analog scale and Short Form-36 were also measured, and are reported in detail elsewhere (21).

Safety assessments

Safety assessments included reporting of all treatment-emergent adverse events (TEAEs), clinical laboratory tests (hematology, chemistry, and urinalysis), vital sign measurements (pulse and blood pressure), physical examination (including body weight), 12-lead electrocardiograms (ECGs), rating scales for EPS [Abnormal Involuntary Movement Scale (AIMS) (22), Barnes Akathisia Rating Scale (BARS) (23), and Simpson-Angus Scale (SAS)

(24)], assessment of depressive symptoms using the Montgomery-Åsberg Depression Rating Scale (MADRS) (25), assessment of suicidality using the Scale for Suicidal Ideation (SSI) (26), evaluation of the proportion of patients who 'switched to depression' (defined as a MADRS score of at least 18 with an increase from baseline of ≥ 4 points at any two consecutive assessments or at the last observation), and assessment of rebound (an increase in CGI-BP-S score for overall bipolar illness of at least 2 points from the end-of-study visit) at the time of post-treatment follow-up.

Statistical analyses

The primary and all other efficacy analyses, except for the noninferiority analysis of the change from baseline to the 12-week endpoint in YMRS total score, were performed on the intent-to-treat (ITT) analysis set. The ITT analysis set included all randomized patients who received at least one dose of double-blind study drug and had both the baseline and at least one postbaseline assessment. The noninferiority analysis of the change from baseline to the 12-week endpoint in YMRS total score was performed on the per-protocol (PP) analysis set. The PP analysis set consisted of randomized patients who had both a baseline and at least one postbaseline YMRS assessment during the acute and maintenance double-blind phases and who did not have major protocol violations. Patients randomly assigned to placebo in the acute phase were not included in the noninferiority analysis. Last-observation-carried-forward (LOCF) approach was used to impute missing visit data for both analysis sets.

The overall type I error rate for testing the paliperidone ER dose versus placebo was at the two-sided 5% level for the primary (YMRS) and the key secondary (GAF) endpoint using a sequential testing strategy (27). For the primary efficacy measure (change from baseline in YMRS total score at the 3-week endpoint), paliperidone ER and placebo groups were compared at the 5% level (two-tailed). If the results were positive for the primary measure, then the key secondary variable (change from baseline in GAF score at the 3-week endpoint) was also tested at the 5% level (two-tailed). For the change from baseline in YMRS score, GAF score, and PANSS score at the 3-week endpoint, the least-squares means (LSMs) for paliperidone ER and placebo were estimated and compared using an analysis of covariance (ANCOVA) model with treatment (placebo and paliperidone ER) and country as factors and baseline score as a covariate.

For CGI-BP-S score, the p-value for the test of a difference between the paliperidone ER treatment group and placebo was produced using an ANCOVA model on the ranks of the change from baseline with treatment (placebo and paliperidone ER groups) and country as factors and baseline score as a covariate. Differences in responder rate and remission rate between the paliperidone ER treatment group and placebo were evaluated using a Cochran-Mantel-Haenszel test controlling for country.

Quetiapine was used in the acute treatment phase to establish assay sensitivity. For assessments at the 3-week endpoint, pairwise comparisons were performed between quetiapine and placebo, and quetiapine and paliperidone ER, using the same ANCOVA model that was used for the primary efficacy analysis (paliperidone ER and placebo), but with appropriate treatment groups (i.e., either quetiapine and placebo or quetiapine and paliperidone ER).

At the completion of the maintenance phase, a noninferiority analysis was used to demonstrate that paliperidone ER is no worse than quetiapine by the predefined margin of 4 points on the change from baseline to the 12-week endpoint in YMRS total score. The point estimate and two-sided 95% confidence interval (CI) were obtained from an ANCOVA model with treatment (paliperidone ER and quetiapine) and country as factors, and baseline YMRS score as covariate. Noninferiority of paliperidone ER to quetiapine was to be concluded if the lower limit of the two-sided 95% CI exceeded −4 (the prespecified margin). All secondary analyses were performed at the 5% level (two-tailed) across the treatment groups with no adjustment for multiplicity.

The safety analyses were performed on the safety analysis set that included all randomized patients who received at least one dose of double-blind study drug. The change from baseline in MADRS and SSI scores between placebo and paliperidone ER, and between quetiapine and placebo, at the 3-week endpoint, and between paliperidone ER and quetiapine at the 3-week as well as the 12-week endpoint, were analyzed using an ANCOVA model with treatment and country as factors and baseline scores as a covariate. The difference between paliperidone ER and placebo, and between quetiapine and placebo at the 3-week endpoint, and between paliperidone ER and quetiapine at the 12-week endpoint, in the proportion of patients who 'switched to depression', was evaluated using a Cochran-Mantel-Haenszel test controlling for country.

Sample size determination

The primary comparison was between paliperidone ER and placebo groups at the 3-week endpoint. The sample size was based on the assumption of a treatment difference of at least 6 points (with an SD of 12) in the change from baseline in YMRS total score between paliperidone ER and placebo. Based on a 2:1 allocation, 192 patients were required (128 in the paliperidone ER and 64 in the placebo group) to attain a power of 90% at the 5% (two-tailed) level of significance. This sample size also provided 90% power to detect a treatment difference of at least 7 points in the change from baseline to endpoint in GAF score (the key secondary endpoint) between paliperidone ER and placebo, assuming an SD of 14. A final sample size of 136 patients in the paliperidone ER group and 68 patients in the placebo group was determined after adjusting for a rate of 6% for patients who would not have either baseline or postbaseline efficacy assessments at the end of 3 weeks.

For the noninferiority analysis of paliperidone ER and quetiapine at the 12-week endpoint the assumption was that the SD for the change in YMRS total score would be 12 and that there would be a true difference of 0 between paliperidone ER and quetiapine. A total of 142 patients per treatment group were required to demonstrate [with 80% power at a 5% (two-tailed) significance level] that paliperidone ER was no worse than quetiapine by 4 points in the change in YMRS total score from baseline at the 12-week endpoint. Assuming 75% of patients randomly assigned to paliperidone ER or quetiapine were evaluable for the PP analysis, 190 patients each for the paliperidone ER and quetiapine treatment groups were required. Therefore, for the study to meet its objectives at both the primary 3-week endpoint (superiority to placebo) and secondary 12-week endpoint (noninferiority to quetiapine), 475 patients needed to be randomly assigned (in a 2:2:1 ratio) to each study drug (190 each for the paliperidone ER and quetiapine groups, and 95 for the placebo group).

Results

Patient disposition and characteristics

Of the 643 patients screened, 493 met eligibility criteria and were randomly assigned to the treatment groups. Of the 493 randomized patients, 232 completed the entire 12-week study. The most

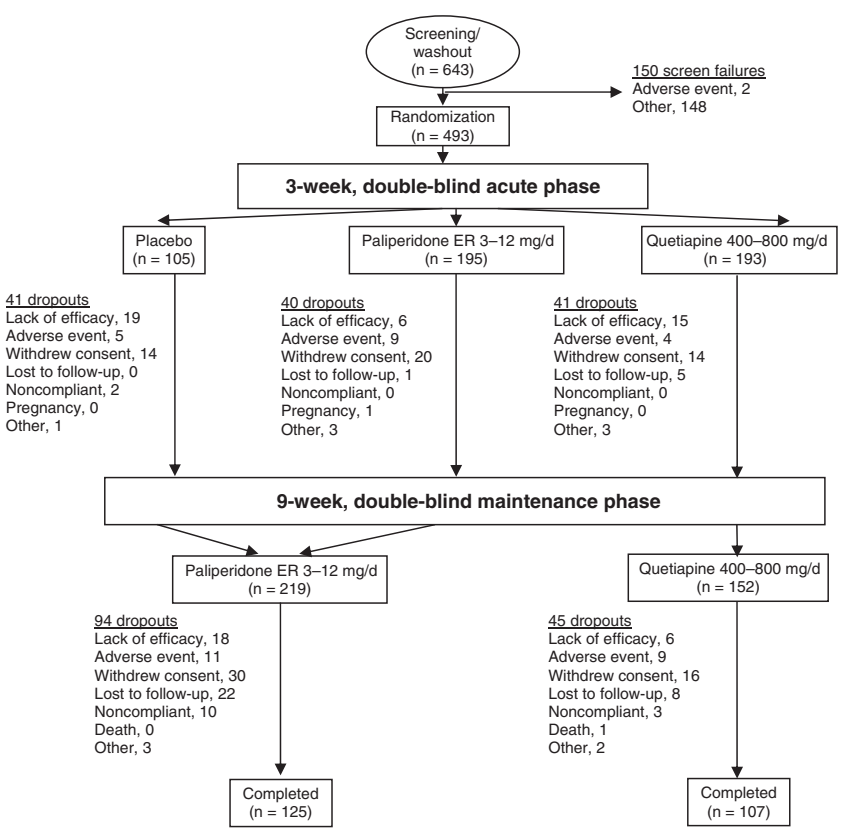

Fig. 1. Patient disposition in the combined acute and maintenance double-blind phases of the study (all randomized analysis set). The *other* reason for screen failures was patients not meeting eligibility criteria. ER = extended-release.

common reasons for patient withdrawal were withdrawal of consent (19%) and lack of efficacy (13%) (Fig. 1). The safety analysis set included 491 patients, the ITT analysis set included 486 patients, and the PP analysis set included 418 patients. A total of 68 (14%) patients in the ITT analysis set had at least one major protocol deviation during the combined acute and maintenance double-blind phases: the most common reasons were randomized patients with selection criteria not met (n = 29), treatment deviation (n = 21), and use of excluded concomitant medication (n = 19).

Baseline and demographic characteristics were comparable across the three treatment groups in the ITT analysis set (Table 1), and the distribution of baseline and demographic characteristics in the PP analysis set was generally similar to the ITT analysis set. Patients had a mean (SD) age of 39 (10.9) years, 58% were men, and 68% were white. All patients (except one in the placebo group who had erroneously been considered to have bipolar disorder) had a current diagnosis of bipolar I disorder (65% with current episode manic, and 35% with current episode mixed), and 21% of patients had severe episodes with psychotic features (DSM-IV criteria) (16). The majority of patients were moderately (56%) or markedly (30%) ill, based on baseline CGI-BP-S scores. A majority (62%) of patients had used an antipsychotic drug within the three months before the study start (54% on placebo, 64% on paliperidone ER, and 65% on quetiapine).

The mean (SD) duration of hospitalization during the acute treatment phase was 10.4 (5.66) days and was comparable across treatment groups. Benzodiazepines (primarily lorazepam, diazepam, and clonazepam) were used as rescue medication by 64% of patients at baseline, which decreased to 53% of patients during the 12-week study. During the acute treatment phase, benzodiazepine use was more common in the placebo group (63%) than in the paliperidone ER (54%) and quetiapine (46%) groups. The mean (SD) duration of exposure to study drug (safety analysis set) was 38 (33.0) days

Table 1. Demographic and baseline characteristics (intent-to-treat analysis set)

	Placebo (n = 104)	Paliperidone ER (n = 190)	Quetiapine (n = 192)
Age (years), mean (SD)	38 (10.0)	40 (11.3)	39 (11.0)
Sex			
Male, n (%)	55 (53)	110 (58)	115 (60)
Race, n (%)			
White	71 (68)	126 (66)	133 (69)
Black	21 (20)	42 (22)	40 (21)
Asian	10 (10)	19 (10)	19 (10)
Other[a]	2 (2)	3 (2)	0 (0)
BMI, (kg/m^2), mean (SD)	29 (7.6)	28 (6.3)	28 (6.4)
Type of bipolar I disorder, n (%)[b]			
Manic episode	61 (59)	133 (70)	121 (63)
Mixed episode	43 (41)	57 (30)	71 (37)
Prior mood episodes, n (%)			
One	8 (8)	10 (5)	13 (7)
Two	19 (18)	26 (14)	26 (14)
Three	14 (13)	38 (20)	39 (20)
Four or more	63 (61)	116 (61)	114 (59)
Current episode, n (%)			
Severe with psychotic features	19 (18)	35 (18)	48 (25)
Duration of current episode (days), mean (SD)	28 (42.6)	19 (29.7)	26 (59.1)
Baseline CGI-BP-S, n (%)			
Minimally and mildly ill	4 (4)	9 (5)	8 (4)
Moderately ill	68 (65)	100 (53)	105 (55)
Markedly ill	25 (24)	66 (35)	56 (29)
Severely and very severely ill	7 (7)	15 (8)	23 (12)
YMRS score, mean (SD)	27 (5.0)	27 (5.0)	28 (5.1)
GAF score, mean (SD)	49 (11.2)	50 (10.4)	49 (11.5)
MADRS score, mean (SD)	12 (7.8)	11 (7.1)	12 (7.6)

ER = extended-release; BMI = body mass index; CGI-BP-S = Clinical Global Impression-Bipolar Disorder-Severity Scale; YMRS = Young Mania Rating Scale; GAF = Global Assessment of Functioning; MADRS = Montgomery-Åsberg Depression Rating Scale.
[a]Other includes American Indian, Alaskan Native, or any other.
[b]One patient in the placebo group had erroneously been considered to have bipolar disorder, current manic episode, and was subsequently determined to be in violation of protocol.

for the placebo/paliperidone ER group, 53 (33.8) days for the paliperidone ER group, and 56 (34.4) days for the quetiapine group; the median mode dose was 9 mg for the paliperidone ER group and 600 mg for the quetiapine group during the acute treatment phase; and 6 mg for the placebo/paliperidone ER group, 9 mg for the paliperidone ER group, and 600 mg for the quetiapine group during the 12 weeks of treatment.

Efficacy

YMRS scores. The mean (SD) change from baseline to the 3-week endpoint in YMRS total score was −7.4 (10.74) in the placebo group, −13.2 (8.68) in the paliperidone ER group, and −11.7 (9.28) in the quetiapine group. The mean standard error (SE) changes over time from baseline to the 3-week endpoint in YMRS total score is shown in Figure 2 for all three treatment groups. Paliperidone ER was superior to placebo in the reduction in YMRS scores at the 3-week endpoint (LSM difference from placebo −5.5; 95% CI: −7.57; −3.35; $p < 0.001$; primary endpoint). The difference in LSMs (95% CI) for the change from baseline in YMRS score at the 3-week endpoint between quetiapine and placebo was −4.2 (−6.45; −1.95; $p < 0.001$), and between quetiapine and paliperidone ER was 1.5 (−0.28; 3.22; $p = 0.099$). Although the placebo group contained a greater proportion of patients with a mixed episode at baseline than the paliperidone ER group (Table 1), a post-hoc analysis of the primary efficacy measure demonstrated no discernable effect of this difference in proportion of patients. Including baseline diagnosis—*manic or mixed*—as an additional covariate in the primary ANCOVA model showed that the difference between the paliperidone ER and placebo groups remained essentially unchanged, and the variable (baseline diagnosis) was not statistically significant ($p = 0.310$).

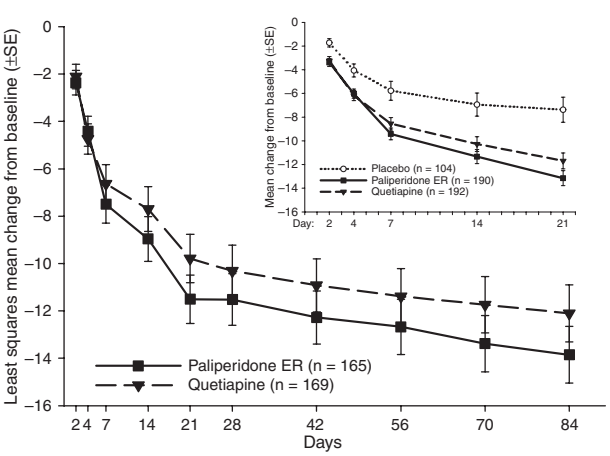

Fig. 2. Least-squares mean change from baseline [± standard error (SE)] in total Young Mania Rating Scale (YMRS) score over time [last observation carried forward (LOCF)] during the combined acute and maintenance double-blind phases (per-protocol analysis set). Insert: Mean changes (± SE) in YMRS total score over time (LOCF) during just the acute double-blind phase (intent-to-treat analysis set). ER = extended-release.

The mean (SD) change from baseline to the 12-week endpoint in YMRS total score was −15.2 (10.26) in the paliperidone ER group and −13.5 (11.02) in the quetiapine group (secondary endpoint). The difference in LSMs (95% CI) for the change in YMRS total score at the 12-week endpoint between quetiapine and paliperidone ER was 1.7 (−0.47; 3.96) (Fig. 2). As the lower limit of the 95% CI was greater than −4 (the prespecified noninferiority margin), paliperidone ER was considered noninferior to quetiapine.

GAF scores. The mean (SD) change from baseline to the 3-week endpoint in GAF score (key secondary endpoint) was 6.7 (13.56) in the placebo group, 12.2 (11.17) in the paliperidone ER group, and 11.6 (11.96) in the quetiapine group. In both the paliperidone ER and quetiapine groups, GAF scores improved significantly more than in the placebo group ($p < 0.001$).

The mean (SD) change from baseline to the 12-week endpoint in GAF score was 14.9 (14.76) in the paliperidone ER group and 15.8 (15.19) in the quetiapine group. The point estimate (95% CI) for the difference in LSMs between paliperidone ER and quetiapine groups for the change in GAF score was 1.0 (−2.00; 3.91; $p = 0.525$), indicating no difference between the two treatment groups.

PANSS and CGI-BP-S scores. At the 3-week endpoint, both PANSS total score and CGI-BP-S scores improved significantly in the paliperidone ER and quetiapine groups compared with placebo (Table 2). PANSS and CGI-BP-S scores showed no difference between the paliperidone ER and quetiapine groups at the 12-week endpoint (Table 2).

Onset of therapeutic effect, responder rate, and remission rate. Paliperidone ER and quetiapine groups improved significantly versus placebo ($p < 0.05$) in YMRS total scores as early as day 2 and at every subsequent time point until day 21. The difference between paliperidone ER and placebo in the LSM change in YMRS total score from baseline (95% CI) on day 2 was −1.6 (−2.5; −0.6). At the 3-week endpoint, the percentage of

Table 2. Change from baseline in PANSS and CGI-BP-S scores at the 3-week and 12-week endpoints (intent-to-treat analysis set)

	3-week endpoint			12-week endpoint		
	Placebo	Paliperidone ER	Quetiapine[a]	PLA/ PALI-ER[b]	PALI-ER/ PALI-ER	QUET/QUET
PANSS, mean (SD)	(n = 95)	(n = 173)	(n = 178)	(n = 95)	(n = 173)	(n = 178)
Baseline	58.3 (14.34)	57.7 (14.65)	57.8 (13.47)	58.3 (14.34)	57.7 (14.65)	57.8 (13.47)
Change from baseline	−5.3 (11.90)	−9.2 (11.13)	−8.1 (10.77)	−4.8 (12.15)	−8.7 (12.46)	−9.9 (12.48)
p-value	–	0.002	0.015	–	–	0.277
LSM difference (95% CI)	–	−4.3 (−6.95; −1.60)[c]	−3.16 (−5.71; −0.61)[d]	–	–	−1.3 (−3.77; 1.08)[e]
CGI-BP-S, median [range]	(n = 104)	(n = 190)	(n = 192)	(n = 104)	(n = 190)	(n = 192)
Baseline	4.0 [3–7]	4.0 [3–6]	4.0 [2–6]	4.0 [3–7]	4.0 [3–6]	4.0 [2–6]
Change from baseline	−0.5 [−3 to 2]	−2.0 [−4 to 2]	−1.0 [−4 to 2]	−1.0 [−4 to 2]	−2.0 [−5 to 1]	−2.0 [−5 to 2]
p-value	–	< 0.001[f]	< 0.001[f]	–	–	0.723
LSM difference (95% CI)	–	–	–	–	–	0 (−0.22; 0.32)[e]

For both PANSS and CGI-BP-S scores, negative change in the score indicates improvement. PANSS = Positive and Negative Syndrome Scale; CGI-BP-S = Clinical Global Impression-Bipolar Disorder-Severity Scale; ER = extended-release; PLA = placebo; PALI = paliperidone; QUET = quetiapine; LSM = least-squares means; CI = confidence interval.
[a]The protocol considered quetiapine only for assay sensitivity at week 3.
[b]Patients who switched from placebo to paliperidone ER were not included in the efficacy analysis at the 12-week endpoint.
[c]Paliperidone ER minus placebo.
[d]Quetiapine minus placebo.
[e]Quetiapine minus paliperidone ER.
[f]p-value based on the intent-to-treat last observation carried forward rank-based analysis.

responders was higher ($p < 0.001$) in the paliperidone ER group (55.8%, 106/190) versus placebo (34.6%, 36/104). The percentage of responders at the 3-week endpoint in the quetiapine group was 49% (94/192).

The percentage of responders at the 12-week endpoint was 64.7% (123/190) for the paliperidone ER group and 57.8% (111/192) for the quetiapine group. There was no difference in the responder rate between the paliperidone ER and quetiapine groups [point estimate of relative risk (95% CI): 1.1 (0.96; 1.30)]. Among the patients initially assigned to paliperidone ER, 100 (94.3%) of the 106 responders at the 3-week endpoint maintained their response at the 12-week endpoint, and an additional 23 (27.4%) of the remaining 84 patients achieved response at the 12-week endpoint.

At the 3-week endpoint, there was a significantly higher ($p < 0.001$) percentage of remitters in the paliperidone ER group (52.1%, 99/190) compared with the placebo group (28.8%, 30/104). The percentage of remitters was 47.4% (91/192) in the quetiapine group.

At the 12-week endpoint, the percentage of remitters was 62.1% (118/190) in the paliperidone ER group and 56.3% (108/192) in the quetiapine group. There was no difference in the relative risk of remission between paliperidone ER and quetiapine groups [point estimate (95% CI): 1.1 (0.95; 1.29)]. Among the patients initially assigned to paliperidone ER, 92 (92.9%) of the 99 remitters at the 3-week endpoint maintained remission at the 12-week endpoint, and an additional 26 (28.6%) of the remaining 91 patients achieved remission at the 12-week endpoint.

Slightly fewer patients would need to be treated with paliperidone ER compared with quetiapine, based on the number-needed-to-treat (NNT) (28), to achieve a clinical response (defined as ≥ 50% reduction from baseline in YMRS total score) in one patient at the 3-week endpoint (Table 3).

Table 3. Effect size and number-needed-to-treat (NNT) for response and remission at the 3-week endpoint

	Paliperidone ER	Quetiapine
Effect size	0.623	0.450
NNT for response (95% CI)	5 (4; 11)	7 (4; 40)
NNT for remission (95% CI)	5 (3; 9)	6 (4; 15)

ER = extended-release; CI = confidence interval.

Safety

During the 3-week treatment period, TEAEs occurred with similar frequency in the placebo (63%) and paliperidone ER groups (65%), and with slightly higher frequency in the quetiapine group (77%). The common (i.e., occurring in ≥ 5% of patients in any treatment group) TEAEs that occurred more frequently (i.e., ≥ 3% difference) in the placebo group compared with the paliperidone ER group were nausea (12% versus 2%), diarrhea (5% versus 1%), and mania (5% versus 1%); and the TEAEs that occurred more frequently (i.e., ≥ 3% difference) in the paliperidone ER group versus placebo were somnolence (10% versus 4%), akathisia (8% versus 3%), hypertonia (5% versus 1%), constipation (5% versus 2%), and dyspepsia (5% versus 1%). Overall, during the 12-week treatment period, TEAEs occurred with similar frequency in the placebo/paliperidone ER (71%) and paliperidone ER groups (70%), and with slightly higher frequency in the quetiapine group (82%). The most common (i.e., occurring in ≥ 5% of patients in any treatment group) TEAEs in the three treatment groups at the end of the 12-week treatment period are shown in Table 4. Most TEAEs in all treatment groups in both the acute and maintenance phases were considered by the investigators to be mild or moderate in severity.

During the 3-week treatment period, serious TEAEs were reported in 18 patients, and TEAEs leading to discontinuation were reported in 22 patients, with similar incidence among the three treatment groups. During the 12-week treatment period, serious TEAEs were reported in 38 patients (similar incidence among the treatment groups), and TEAEs leading to discontinuation were reported in 37 patients [slightly higher incidence in the paliperidone ER group (9%) compared with placebo/paliperidone ER (7%) and quetiapine (6%) groups]. The serious TEAEs that occurred during the 3-week (2–3% of patients in all groups) and 12-week treatment periods (6% of patients in all groups) were most often related to the underlying psychiatric disorder of patients. Suicidal ideation as a serious TEAE was reported in one paliperidone ER patient and two quetiapine patients in the 12-week study.

There was one death reported in the study (suicide during the maintenance phase, quetiapine

Table 4. Treatment-emergent adverse events that occurred in at least 5% of patients in any of the active treatment groups during the 12-week treatment period (safety analysis set)

	Acute treatment phase			Maintenance phase		
Adverse events	Placebo (n = 105)	Paliperidone ER (n = 194)	Quetiapine (n = 192)	PLA/PALI-ER (n = 105)	Paliperidone ER (n = 194)	Quetiapine (n = 192)
Total	**66 (63)**	**127 (65)**	**147 (77)**	**75 (71)**	**136 (70)**	**157 (82)**
Headache	13 (12)	24 (12)	25 (13)	14 (13)	31 (16)	26 (14)
Somnolence	4 (4)	19 (10)	35 (18)	4 (4)	19 (10)	41 (21)
Akathisia	3 (3)	16 (8)	6 (3)	4 (4)	19 (10)	6 (3)
Sedation	5 (5)	15 (8)	30 (16)	5 (5)	17 (9)	32 (17)
Dizziness	5 (5)	12 (6)	23 (12)	5 (5)	15 (8)	24 (13)
Hypertonia	1 (1)	9 (5)	2 (1)	1 (1)	9 (5)	2 (1)
Lethargy	1 (1)	4 (2)	10 (5)	2 (2)	4 (2)	12 (6)
Drooling	0 (0)	8 (4)	0 (0)	2 (2)	12 (6)	0 (0)
Tremor	2 (2)	8 (4)	4 (2)	3 (3)	10 (5)	5 (3)
Constipation	2 (2)	10 (5)	11 (6)	3 (3)	12 (6)	14 (7)
Dyspepsia	1 (1)	10 (5)	12 (6)	3 (3)	11 (6)	15 (8)
Dry mouth	7 (7)	9 (5)	29 (15)	7 (7)	10 (5)	33 (17)
Nausea	13 (12)	3 (2)	3 (2)	15 (14)	5 (3)	6 (3)
Diarrhea	5 (5)	2 (1)	4 (2)	6 (6)	5 (3)	7 (4)
Toothache	3 (3)	2 (1)	5 (3)	5 (5)	3 (2)	7 (4)
Insomnia	10 (10)	14 (7)	13 (7)	11 (10)	16 (8)	16 (8)
Mania	5 (5)	2 (1)	6 (3)	5 (5)	4 (2)	9 (5)
Depression	1 (1)	3 (2)	0 (0)	4 (4)	11 (6)	0 (0)
Agitation	4 (4)	5 (3)	5 (3)	5 (5)	6 (3)	6 (3)
Fatigue	2 (2)	8 (4)	9 (5)	2 (2)	8 (4)	10 (5)
Increased appetite	0 (0)	4 (2)	9 (5)	1 (1)	6 (3)	10 (5)
Myalgia	4 (4)	3 (2)	0 (0)	5 (5)	3 (2)	1 (1)
Weight increased	2 (2)	6 (3)	8 (4)	8 (8)	8 (4)	18 (9)
Tachycardia	1 (1)	5 (3)	7 (4)	2 (2)	6 (3)	9 (5)

Values presented as n (%). ER = extended-release; PLA = placebo; PALI = paliperidone.

group) and another death reported five days after withdrawal from the study (due to complications of a suicide attempt, placebo/paliperidone ER group). Both were considered as possibly related to the study drug.

Of the overall TEAEs, adverse events (AEs) suggestive of depression were reported in 5 (5%) patients in the placebo/paliperidone ER group, 14 (7%) patients in the paliperidone ER group, and none in the quetiapine group. Major depression was reported in one patient in the paliperidone ER group. During the 3-week treatment period, EPS-related AEs that occurred more frequently in the paliperidone ER group (≥ 3% difference versus placebo) were akathisia, hypertonia, drooling, extrapyramidal disorder, and muscle spasms. During the 12-week treatment period, those that occurred with a higher incidence in the paliperidone ER group (≥ 3% difference compared with quetiapine) were akathisia, hypertonia, and drooling (Table 4). The EPS-related AEs were mild or moderate in severity; none was serious. One patient in the paliperidone ER group discontinued during the maintenance phase as a result of an EPS-related AE. One patient in the paliperidone ER group experienced mild tardive dyskinesia during the acute treatment phase. No new TEAEs of tardive dyskinesia were reported during the maintenance phase.

The median SAS global scores and AIMS total score were 0 in all treatment groups at baseline and at the 3-week and 12-week endpoints. The percentage of patients who experienced mild akathisia, based on the BARS global clinical rating scores, was higher in the paliperidone ER group at the 3-week (5%) and 12-week (3%) endpoints compared with baseline (2%). In addition, severe akathisia was reported for one patient at the 3-week and 12-week endpoints in the paliperidone ER group and none was reported in the placebo or quetiapine groups. The percentage of patients receiving anticholinergic medications during the acute treatment phase was 17% in the paliperidone ER group, 5% in the placebo group, and 7% in the quetiapine group, and at any time during the acute treatment and maintenance phases was 19% in the paliperidone ER group, 8% in the placebo/paliperidone ER group, and 10% in the quetiapine group.

Treatment-emergent glucose-related AEs were rare [occurring in 1 (1%) patient assigned to the paliperidone ER group, 2 (2%) patients assigned to the placebo/paliperidone ER group, and 3 (2%) patients assigned to the quetiapine group] and not serious, and none led to discontinuation from the study. During the study, 10 (5%) patients in the paliperidone ER group, and 3 (3%) patients in the placebo/paliperidone ER group experienced potentially prolactin-related AEs, versus 4 (2%) patients in the quetiapine group. No potentially prolactin-related AE was reported as serious or led to discontinuation of study drug.

At the 3-week endpoint, mean (SD) changes from baseline in serum prolactin levels were 24.61 (23.98) ng/mL (men) and 89.77 (81.47) ng/mL (women) in the paliperidone ER group, versus −1.03 (14.08) ng/mL (men) and 7.15 (31.82) ng/mL (women) in the placebo group. The corresponding mean (SD) changes in prolactin levels in the quetiapine group were −1.32 (19.9) ng/mL in men and 0.3 (30.92) ng/mL in women. The proportion of patients with treatment-emergent prolactin levels outside the laboratory reference range at any time during the acute treatment and maintenance phases was higher in both men (63%, 61/97) and women (61%, 43/71) in the paliperidone ER group compared with either the placebo/paliperidone ER (men: 30%, 14/47; women: 30%, 13/43) or quetiapine (men: 17%, 17/98; women: 16%, 11/67) groups. During the acute treatment and maintenance phases, more patients in the paliperidone ER and quetiapine groups had pulse rates above clinically significant limits compared with the placebo/paliperidone ER group. Abnormally high heart rates were reported more frequently in patients assigned to the paliperidone ER (20%) and quetiapine (19%) groups than the placebo/paliperidone ER group (10%). There were no clinically relevant differences in laboratory parameters (other than serum prolactin), vital signs (other than pulse), and ECG recordings (other than heart rate) between different treatment groups during the study.

The mean change (SD) in body weight from baseline to the 3-week endpoint was 0.6 (2.5) kg for placebo, 1.1 (2.1) kg for paliperidone ER, and 1.1 (3.5) kg for quetiapine; and from baseline to the 12-week endpoint was 1.2 (3.0) kg for placebo/paliperidone ER, 1.5 (2.9) kg for paliperidone ER, and 2.0 (4.6) kg for quetiapine. Weight increase of ≥ 7% from baseline body weight at the 12-week endpoint was more common among patients in the quetiapine group (17%) than in the paliperidone ER (8%) or placebo/paliperidone ER (6%) groups.

Depression and Suicidal Ideation Rating Scale scores

There was a significant improvement in MADRS and SSI scores in the paliperidone ER group compared with the placebo group at the 3-week endpoint (Table 5). At the 12-week endpoint, the improvement in MADRS score was greater in the

Table 5. Mean (SD) change from baseline in MADRS and SSI scores at the 3-week and 12-week endpoints (safety analysis set)

	3-week endpoint			12-week endpoint		
	Placebo (n = 105)	Paliperidone ER (n = 194)	Quetapine[a] (n = 192)	PLA/ PALI-ER[b] (n = 105)	PALI-ER/ PALI-ER (n = 194)	QUET/QUET (n = 192)
MADRS score	(n = 100)	(n = 187)	(n = 187)	(n = 100)	(n = 187)	(n = 187)
Baseline	12.4 (7.82)	11.2 (7.08)	11.5 (7.37)	12.4 (7.82)	11.2 (7.08)	11.5 (7.37)
Change from baseline	−2.2 (7.42)	−4.0 (6.23)	−4.0 (6.38)	−1.2 (7.86)	−2.0 (8.81)	−4.2 (7.41)
p-value	–	< 0.001	–	–	–	–
LSM difference (95% CI)	–	−2.4 (−3.81; −1.02)[c]	−2.3 (−3.73; −0.91)[d]	–	–	−2.1 (−3.51; −0.62)[e]
SSI total score	(n = 95)	(n = 174)	(n = 178)	(n = 95)	(n = 174)	(n = 178)
Baseline	0.4 (1.47)	0.5 (1.79)	0.6 (2.42)	0.4 (1.47)	0.5 (1.79)	0.6 (2.42)
Change from baseline	0.2 (2.57)	−0.2 (1.38)	−0.2 (2.55)	0.2 (2.33)	0.1 (2.18)	−0.1 (2.76)
p-value	–	0.033	–	–	–	–
LSM difference (95% CI)	–	−0.4 (−0.81; −0.03)[c]	−0.3 (−0.80; 0.14)[d]	–	–	−0.1 (−0.50; 0.31)[e]

Negative change in MADRS and SSI scores indicates improvement. MADRS = Montgomery-Åsberg Depression Rating Scale; SSI = Scale for Suicidal Ideation; ER = extended-release; PLA = placebo; PALI = paliperidone; QUET = quetiapine; LSM = least-squares means; CI = confidence interval.
[a]The protocol considered quetiapine only for assay sensitivity at week 3.
[b]Patients who switched from placebo to paliperidone ER were not included in the statistical analysis at the 12-week endpoint.
[c]Paliperidone ER minus placebo.
[d]Quetiapine minus placebo.
[e]Quetiapine minus paliperidone ER.

quetiapine group compared with the paliperidone ER group; the change in SSI scores was not significantly different in the quetiapine versus the paliperidone ER group (Table 5). The percentage of patients who 'switched to depression' at the 3-week endpoint was not significantly different ($p = 0.104$) in the paliperidone ER group (4.3%) versus placebo (9.0%); the percentage was significantly less ($p = 0.017$) in the quetiapine group (2.7%) versus placebo. At the 12-week endpoint, the percentage of patients who 'switched to depression' was 18.0% in the placebo/paliperidone ER group, 13.9% in the paliperidone ER group, and 7.5% in the quetiapine group [the difference between paliperidone ER and quetiapine was significant ($p = 0.044$)].

Rebound, defined on the basis of the CGI-BP-S score at follow-up visit, occurred in 1 (1.5%) patient in the placebo/paliperidone ER group, 4 (3.3%) patients in the paliperidone ER group, and 8 (5.8%) patients in the quetiapine group.

Discussion

In this trial in bipolar I disorder patients with acute manic and mixed episodes, paliperidone ER was superior to placebo on the primary efficacy measure of reduction in YMRS total scores at the end of 3 weeks of double-blind treatment. YMRS total scores improved significantly in the paliperidone ER group compared with placebo as early as day 2 (difference of 1.6 YMRS units), and at every subsequent time point during the 3-week treatment period. The three-arm design, including placebo and an active comparator, was used to evaluate the sensitivity of the study and to ensure that the drug under investigation was effective compared with standard treatment. Placebo control is needed as a viable and necessary standard, especially in studies in acute mania, due to the high rates of placebo response observed (29, 30). In this trial, patients with a mixed episode who were assigned to placebo tended to have a high placebo response, while the effect of treatment with paliperidone ER was fairly similar across patients who experienced either an acute manic or mixed episode. Quetiapine was chosen as the active comparator because it has proven efficacy in the treatment of mania (31, 32).

Paliperidone ER was noninferior to quetiapine for the secondary efficacy measure of reduction in YMRS scores at the end of the 12-week treatment period. A margin of 4 units to determine noninferiority was prespecified based on a combination of statistical reasoning and clinical judgment. In a 12-week, placebo-controlled study, the estimated benefit of quetiapine relative to placebo was 11.3 points on the YMRS at the 12-week endpoint, and

the estimated lower limit of the 95% CI (assuming an SD of 12) for the treatment benefit was 7.96 (31). The treatment benefit of paliperidone ER after 12 weeks was expected to be close to 11 points on the YMRS based on the clinical data for risperidone in the treatment of acute manic and mixed episodes. Hence, in the current study, a difference in effect of ≤ 4 points on the YMRS was considered to represent no important clinical difference in efficacy.

Clinically meaningful improvements in GAF, CGI-BP-S, and PANSS scores were also observed with paliperidone ER, with significant improvements, versus placebo, seen at the end of the 3-week period and improvements similar to quetiapine seen at the end of the 12-week treatment period. The percentage of responders and remitters was significantly higher with paliperidone ER compared with placebo at the 3-week endpoint, and was similar compared with quetiapine at the 12-week endpoint. Of the patients who had not responded to treatment with paliperidone ER at the end of 3 weeks, 27.4% responded at the end of 12 weeks. The NNT for clinical response of 5 with paliperidone ER in this study is comparable to the NNT of 5 observed with olanzapine, risperidone, and aripiprazole in placebo-controlled, short-term (< 6 weeks) trials in acute mania (33). A slightly higher NNT of 6 has been reported for quetiapine (33) and lithium (34), and in this trial the NNT was 7 for quetiapine.

A design limitation inherent in the three-arm design used for this study is that responders to placebo and nonresponders to active treatment at the 3-week endpoint were continued on active medication for an additional 9 weeks, in order to maintain study blind. Although a very similar study design was utilized in recently published studies of aripiprazole as monotherapy in the treatment of mania (35, 36), this may possibly raise ethical concerns, as the condition of some patients could either have improved further, or worsened, while patients continued to be exposed to active medication unnecessarily. However, the 9-week double-blind, continuation phase is important to establish maintenance of effect and provide a better assessment of 'switching to depression'. In addition, the blinded transfer of patients initially assigned to placebo to active medication after 3 weeks limits the duration of exposure to placebo and any associated possible risks, while minimizing the potential impact on the validity of the data collected over a 12-week period in the study. Accordingly, the protocol of this study was approved by all independent ethics committees, institutional review boards, and health authorities concerned.

A flexible dosing regimen of paliperidone ER was used in this study, which allowed investigators to optimize the dosage of paliperidone ER for each patient, thus maximizing therapeutic effect while minimizing any tolerability issues. Flexibly dosed paliperidone ER was tolerable, and the nature of adverse events was similar to those observed in earlier paliperidone ER studies in patients with schizophrenia (11, 13, 14). During the 12-week treatment period, the incidence of TEAEs was similar in the placebo/paliperidone ER and paliperidone ER groups and higher in the quetiapine group. Consistent with the known pharmacology of paliperidone, increases in prolactin levels were observed in both men and women receiving paliperidone ER. The incidence of potentially prolactin-related AEs was higher in the paliperidone ER group compared with the placebo/paliperidone ER and quetiapine groups. Weight increase observed in patients with bipolar disorder is partly related to the prescribed drugs, with the strongest effects seen with drugs such as olanzapine and clozapine (37). In this study, there was a higher mean change from baseline in body weight as well as a greater proportion of patients with weight increase ≥ 7% in the quetiapine group compared with the paliperidone ER and placebo/paliperidone ER groups.

The improvements in MADRS and SSI scores in the paliperidone ER group were significant compared with the placebo group at the end of the 3-week treatment period. At the 12-week endpoint, the change from baseline in MADRS score was greater in the quetiapine group compared with the paliperidone ER group and the change in SSI scores was not different between the two groups.

Paliperidone ER, in a flexible dose-range of 3–12 mg/day, demonstrated efficacy in the treatment of acute mania compared with placebo, with onset of efficacy observed as early as day 2. Paliperidone ER was tolerable, and no new safety findings were reported. Paliperidone ER may offer a new treatment option for patients with bipolar I disorder with acute manic episodes.

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