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Research paper

Rapid onset of treatment effects on psychosis, depression, and mania in patients with acute exacerbation of schizoaffective disorder following treatment with oral extended-release paliperidone

Dong-Jing Fu [a,*], Ibrahim Turkoz [b], Cynthia A. Bossie [a], Hiren Patel [a,1], Larry Alphs [a]

[a] Janssen Scientific Affairs, LLC, 1125 Trenton-Harbourton Road–A32404, Titusville, NJ 08560, USA
[b] Janssen Research & Development, Titusville, NJ, USA

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ABSTRACT

Background: Patients with schizoaffective disorder (SCA) experience complicated interplays of psychotic, depressive, and manic symptoms. Paliperidone extended-release (pali ER) tablets have been shown to be efficacious in these patients, but treatment response has not been studied relative to the onset of effects for these symptom domains.

Methods: In a pooled analysis of data from two 6-week, randomized, placebo-controlled studies, the onset of treatment effects with oral pali ER was evaluated by symptom domain (psychosis, depression, mania) in patients with an acute SCA exacerbation. Subjects were categorized as having prominent psychotic (Positive and Negative Syndrome Scale score >70), depressive (Hamilton Rating Scale for Depression–21 score ≥ 16), or manic (Young Mania Rating Scale score ≥ 16) symptoms at baseline.

Results: Of the 614 patients in these analyses, 597 (97.2%), 411 (66.9%), and 488 (79.5%) had prominent psychotic, depressive, and manic symptoms at baseline, respectively. Pali ER treatment was associated with rapid and significant improvement of all three symptom domains versus placebo within 1 week of initiation, regardless of whether treatment was given as monotherapy or in combination with mood stabilizers and/or antidepressants. Adverse events were similar to those reported in the original published studies.

Limitations: This post hoc analysis of two phase 3 trials requires confirmation in prospective studies.

Conclusion: This pooled analysis suggests that treatment with pali ER is associated with rapid control of psychotic, depressive, and manic symptoms in patients with SCA. Its findings support the benefit of pali ER as a primary treatment for the management of SCA.

1. Introduction

The 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) reaffirms schizoaffective disorder (SCA) as a distinct diagnostic entity characterized by a mix of symptoms, including psychosis, depression, and mania, that are associated with schizophrenia and affective disorders (American Psychiatric Association [APA], 2013). SCA is about one-third as prevalent as schizophrenia (Canuso et al., 2010) and has a prognosis that is generally intermediate to that of schizophrenia and affective disorders (Canuso et al., 2010). SCA can be disabling and requires significant mental health resources (Kent et al., 1995), but treatment with antipsychotic medication can help manage symptoms and improve quality of life for patients with the disorder.

Historically, symptoms of SCA have been managed with symptom-specific concomitant medications that include antipsychotics, mood stabilizers, antidepressants, and anxiolytics (Olfson et al., 2009). More recently, large, well-controlled clinical trials of oral paliperidone extended-release (pali ER), administered as monotherapy or in combination with mood stabilizers and/or antidepressants, has helped establish the drug as a safe, effective, and acute treatment of SCA (Canuso et al., 2010b; Canuso et al., 2010a; Canuso et al., 2010c; Ortho-McNeil-Janssen Pharmaceuticals, Inc., 2011). In addition, a 15-month relapse-prevention study showed once-monthly paliperidone palmitate to be an effective long-term maintenance treatment for SCA when given as monotherapy or in combination with mood stabilizers or antidepressants (Fu et al., 2015).

Because patients with SCA experience various types and severities of psychotic, depressive, and/or manic symptoms, understanding the extent and timing of treatment effects on each of

*Corresponding author.
E-mail address: dfu@its.jnj.com (D.-J. Fu).
[1] Was employed at Janssen Scientific Affairs, LLC, at the time of this analysis.

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these symptom groups and providing insights into the use of concomitant therapies are important for clinical decision-making. This pooled analysis of two large registration trials in acutely exacerbated subjects with SCA evaluated the pattern and timing of onset of pali ER treatment effects for the three primary SCA symptom domains: psychosis, depression, and mania.

2. Methods

2.1. Study design

Pooled data from two 6-week, randomized, placebo-controlled studies of pali ER treatment versus placebo in patients with SCA ($N=614$) were examined in post hoc analyses (Canuso et al., 2010c). Full details of these studies have been reported elsewhere (Canuso et al., 2010b; Canuso et al., 2010a).

Briefly, in study 1 (ClinicalTrials.gov identifier: NCT00412373) (Canuso et al., 2010b), acutely exacerbated subjects with SCA were randomly assigned in a 2:1 ratio to receive 6 mg/day pali ER or placebo. After day 4, the dosage could be adjusted in 3-mg increments in a range of 3 to 12 mg/day. In study 2 (ClinicalTrials.gov identifier: NCT00397033) (Canuso et al., 2010a), acutely exacerbated subjects with SCA were randomly assigned in a 1:1:1 ratio to receive lower-dose pali ER (6 mg/day, with an option to reduce to 3 mg/day), higher-dose pali ER (12 mg/day, with an option to reduce to 9 mg/day), or placebo. Dose adjustments were permitted until day 15 for both studies, after which time no further changes were allowed. Subjects could receive concomitant treatment with mood stabilizers and/or antidepressants if they had been treated with a stable dose within 30 days of screening (Canuso et al., 2010b, 2010a). During screening, all other antipsychotic medications were discontinued in a washout period of 2 to 5 days. Subjects on stable doses of benzodiazepines at study entry could continue at the same dose throughout the study. New use of benzodiazepines was permitted for the first 15 days of the study.

The final protocols of the original studies were approved by participating independent ethics committees or institutional review boards (Canuso et al., 2010b, 2010a). The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki, and each subject provided written informed consent according to local requirements after receiving a full explanation of the study.

2.2. Participants

Subjects in these studies were aged 18 to 65 years with a current diagnosis of SCA, as confirmed by the Structured Clinical Interview for DSM (DSM-IV) Disorders (American Psychiatric Association, 1994). All were experiencing an acute exacerbation of illness and prominent mood symptoms of <4 weeks in duration, as evidenced by the Young Mania Rating Scale (YMRS) (Young et al., 1978) total score of ≥ 16 and/or the Hamilton Rating Scale for Depression, 21-item version (HAM-D-21) (Hamilton, 1960) total score ≥ 16; the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) total score ≥ 60; and the PANSS score ≥ 4 on two or more items (ie, hostility, excitement, tension, uncooperativeness, or poor impulse control) (Canuso et al., 2010c).

For this analysis, subjects were categorized according to whether they displayed prominent psychotic (PANSS score >70), depressive (HAM-D-21 score ≥ 16), or manic (YMRS score ≥ 16) symptoms at baseline. Subjects could be included in more than one category because baseline symptom categories were not mutually exclusive. Specifically, a subject could present with prominent symptoms in more than one of these domains: psychotic, depressive, or manic.

2.3. Assessments

Efficacy of pali ER was assessed using the PANSS, the Clinical Global Impressions–Severity of Illness Scale for Schizoaffective Disorder (CGI-S-SCA), the HAM-D-21, and the YMRS. Assessments were performed at baseline, at day 4, and at weeks 1, 2, 3, 4, and 6 (Canuso et al., 2010b, 2010a).

Analysis end points were changes from baseline to day 4 and changes from baseline to weeks 1, 2, 3, 4, and 6 (end point) in PANSS, HAM-D-21, and YMRS total scores. Responder rates, defined as subjects with a $\geq 50\%$ decrease from baseline in symptom scale scores, were identified. The number of subjects who improved in all three domains (psychosis, depression, and mania) was measured at each time point and evaluated according to treatment type (ie, pali ER or placebo, administered as monotherapy or in combination with mood stabilizers and/or antidepressants). Clinically meaningful improvements in the PANSS, HAM-D-21, and YMRS were assessed and defined as a $\geq 30\%$ improvement (European Medicines Agency and Committee for Medicinal Products for Human Use (CHMP), 2012) or a ≥ 10-point decrease (Leucht et al., 2006) in the PANSS; a $\geq 50\%$ improvement (Furukawa et al., 2007) or ≥ 4-point decrease in the HAM-D-21 (Turkoz et al., 2013); and a $\geq 50\%$ improvement (Kemp et al., 2011) or ≥ 6-point decrease in the YMRS (Turkoz et al., 2013), respectively. Safety assessments for this analysis included adverse event (AE) reporting and were classified according to the Medical Dictionary for Regulatory Activities (MedDRA version 9.0).

2.4. Statistical analysis

The intention-to-treat (ITT) analysis set, defined as subjects who received at least one dose of study medication and had at least one postbaseline efficacy assessment, was used for efficacy and safety assessments. Between-group differences in continuous variables were evaluated using an analysis of covariance model with fixed effects for treatment, concomitant medication strata, study identification (ID), country nested within study ID, and baseline variable. Between-group differences in categorical variables were evaluated using a Cochran–Mantel–Haenszel test that controlled for concomitant medication strata, study ID, and country. Percentage differences were also examined using Fisher's exact test. Analyses of efficacy data involving changes from baseline to each assessment time point used the last-observation-carried-forward approach. No adjustments were made for multiplicity.

3. Results

3.1. Baseline Demographics and Clinical Characteristics

The majority of subjects had overlapping symptoms of psychosis, depression, and mania (Table 1). Of the 614 patients included in these analyses, 597 (97.2%), 411 (66.9%), and 488 (79.5%) had prominent psychotic, depressive, and manic symptoms, respectively. In the overall ITT analysis set, 414 and 200 subjects received pali ER and placebo, respectively. Baseline demographics and clinical characteristics are outlined in Table 1. Regardless of baseline symptoms, the mean age of subjects was 37 years, and approximately 50% were white. All subjects had acute psychotic symptoms at screening, and the majority (97.2%; 597/614) had prominent, continuous psychotic symptoms at the time they were randomly assigned to treatment. Approximately half (44.8%; 275/614) of the subjects were receiving concomitant mood stabilizers and/or antidepressants, with mood stabilizers used by 69.5% (191/275) and antidepressants by 49.1% (135/275) (Canuso et al., 2010c).

Table 1
Baseline demographics and clinical characteristics (ITT population, $N=614$).

Parameter	Prominent psychotic[a] $N=597$		Prominent depressive[a] $N=411$		Prominent manic[a] $N=488$	
	Pali ER $n=402$	Placebo $n=195$	Pali ER $n=282$	Placebo $n=129$	Pali ER $n=328$	Placebo $n=160$
Age, years, mean (SD)	37.3 (9.6)	37.2 (10.2)	37.4 (9.8)	37.1 (10.0)	37.7 (9.7)	37.4 (10.4)
Sex, *n* (%)						
Male	242 (60.2)	117 (60.0)	156 (55.3)	74 (57.4)	202 (61.6)	98 (61.3)
Female	160 (39.8)	78 (40.0)	126 (44.7)	55 (42.6)	126 (38.4)	62 (38.8)
Race, *n* (%)						
White	195 (48.5)	96 (49.2)	140 (49.6)	67 (51.9)	154 (47.0)	80 (50.0)
Black/African American	79 (19.6)	37 (19.0)	69 (24.5)	25 (19.4)	66 (20.1)	32 (20.0)
Asian	124 (30.9)	62 (31.8)	71 (25.2)	37 (28.7)	104 (31.7)	48 (30.0)
Other	4 (1.0)	0 (0)	2 (0.7)	0 (0)	4 (1.2)	0 (0.0)
SCA subtype, *n* (%)						
Depressive	123 (30.8)	66 (33.8)	122 (43.7)	64 (49.6)	57 (17.5)	37 (23.1)
Bipolar	276 (69.2)	129 (66.2)	157 (56.3)	65 (50.4)	268 (82.5)	123 (76.9)
PANSS total score, mean (SD)	94.1 (12.7)	92.3 (11.7)	96.3 (12.7)	94.8 (12.2)	93.3 (13.6)	91.5 (12.2)
YMRS, mean (SD)	24.4 (10.1)	24.2 (10.1)	21.9 (10.2)	20.8 (10.1)	28.3 (7.5)	27.8 (7.5)
HAM-D-21, mean (SD)	20.7 (9.0)	19.7 (8.2)	25.2 (6.6)	24.5 (5.6)	19.1 (9.3)	17.8 (8.0)
Concomitant mood stabilizer/antidepressant use, *n* (%)	178 (44.3)	87 (44.6)	135 (47.9)	67 (51.9)	134 (40.9)	67 (41.9)
Monotherapy, *n* (%)	221 (55.0)	109 (55.9)	148 (52.5)	62 (48.1)	193 (58.8)	94 (58.8)
Suicide history, yes, *n* (%)	123 (30.7)	63 (32.5)	101 (35.8)	51 (39.5)	101 (30.9)	51 (32.1)
Previous hospitalization, *n* (%)	$N=397$	$N=192$	$N=280$	$N=126$	$N=324$	$N=157$
	333 (83.9)	168 (87.5)	234 (83.6)	110 (87.3)	277 (85.5)	139 (88.5)

CGI-S-SCA, Clinical Global Impressions-Severity of Illness Scale for Schizoaffective Disorder; HAM-D-21, Hamilton Rating Scale for Depression, 21-item version; ITT, intent-to-treat; Pali ER, paliperidone extended-release; PANSS, Positive and Negative Syndrome Scale; SCA, schizoaffective disorder; YMRS, Young Mania Rating Scale.

[a]The three groups are not mutually exclusive.

In subjects receiving concomitant mood stabilizers and/or antidepressants vs those receiving monotherapy, the overall mean (standard deviation [SD]) duration of illness was 12.8 (9.2) vs 11.9 (9.6) years. The rate of duration of illness >5 years was 72.6% vs 65.8%, respectively.

In the prominent psychosis subgroup, early withdrawal from the study occurred in 129/402 (32.1%) of pali ER–treated subjects and 82/195 (42.1%) of placebo-treated subjects. The main reasons for pali ER and placebo discontinuation were lack of efficacy (10.1% vs 18.5%) and subject choice (8.4% vs 9.7%). In the prominent depressive subgroup, 97 (34.4%) of pali ER–treated subjects and 56 (43.4%) of placebo-treated subjects withdrew from the study; the main reasons for discontinuation were lack of efficacy (10.3% vs 17.1%) and subject choice (9.5% vs 12.4%). In the prominent manic subgroup, 102 (31.1%) of pali ER–treated subjects and 65 (40.6%) of placebo-treated subjects withdrew from the study; the main reasons for discontinuation (pali ER vs placebo) in this subgroup were also lack of efficacy (9.8% vs 17.5%) and subject choice (8.2% vs 10.6%). The mean (SD) dose in the prominent psychotic, depressive, and manic subgroups was 8.3 (2.6) mg for each group.

3.2. Efficacy in Psychotic, Depressive, and Manic Symptoms

3.2.1. Prominent Psychotic Symptoms

In subjects with prominent psychosis at baseline, significant improvement was observed with pali ER compared with placebo in mean change from baseline in PANSS total score from day 4 to end point (Fig. 1A). A significantly greater proportion of pali ER–treated subjects were PANSS responders (≥50% reduction in PANSS scores from baseline) relative to placebo from week 2 to end point (Fig. 1B). The proportion of subjects with prominent psychosis at baseline who achieved a clinically meaningful improvement from baseline (ie, a 10-point reduction in PANSS total score) in psychotic symptoms throughout the course of therapy is summarized in Fig. 1C. In this patient subgroup, manic and depressive symptoms as measured by the mean change in YMRS and HAM-D-21 scores also significantly improved when compared with placebo from day 4 of treatment ($p \leq .01$ for all time points). Subjects with prominent psychotic symptoms at baseline showed clinically and statistically significant improvement in mean PANSS score compared with placebo beginning at week 1 of therapy, with improvement continuing until week 3, followed by a plateau in clinical response until study end point.

3.2.2. Prominent depressive symptoms

In subjects with prominent depression at baseline, significant improvement was observed with pali ER versus placebo in mean change from baseline in HAM-D-21 score from day 4 to end point ($p < .05$) (Fig. 2A). A significantly greater proportion of pali ER-treated subjects were HAM-D-21 responders (≥ 50% reduction in HAM-D-21 scores from baseline) relative to placebo at weeks 1, 2, and 4 and at end point (Fig. 2B) ($p < .05$ for selected time points). The proportion of subjects with prominent depressive symptoms at baseline who achieved a clinically meaningful improvement in depressive symptoms from baseline to end point is summarized in Fig. 2C. In this patient subgroup, mean change in YMRS and HAM-D-21 scores also significantly improved when compared with placebo from week 1 of treatment ($p < .05$ for all time points). Subjects with prominent depressive symptoms at baseline showed clinically and statistically significant ($p < .05$) improvement in mean HAM-D-21 score compared with placebo, beginning from week 1 of therapy and increasing until week 2, at which time there was a plateau in improvement until end point.

3.2.3. Prominent manic symptoms

In subjects with prominent mania at baseline, significant improvement ($p < .05$) was observed with pali ER versus placebo in mean change from baseline in YMRS score from day 4 to end point (Fig. 3A). A significantly ($p < .05$) greater proportion of pali ER–treated subjects were YMRS responders (≥ 50% reduction in YMRS scores from baseline) relative to placebo from week 2 to end point (Fig. 3B). The proportion of subjects with prominent manic symptoms at baseline who achieved a clinically meaningful improvement from baseline in depressive symptoms throughout the

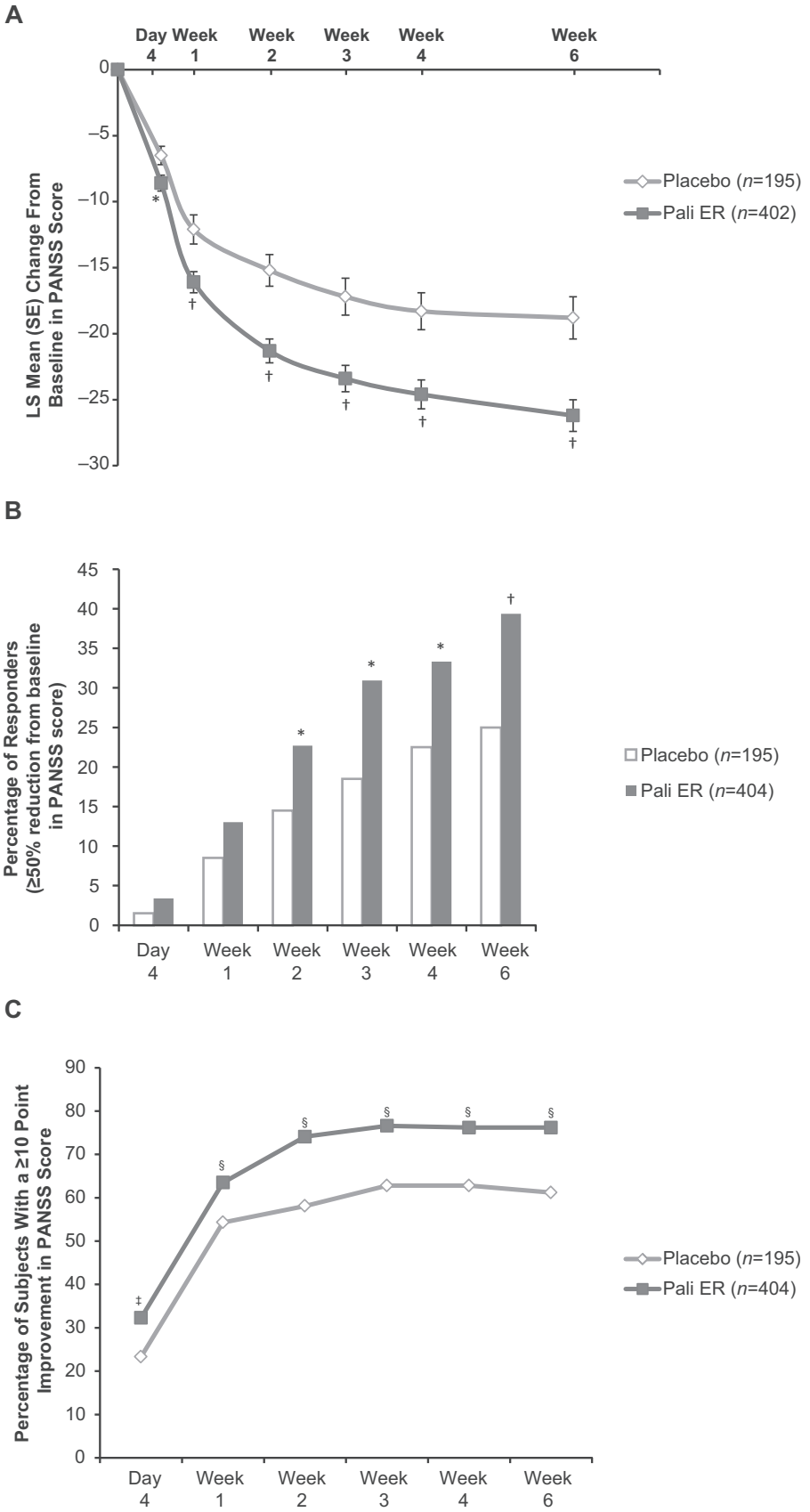

Fig. 1. Subjects with prominent psychotic symptoms (Positive and Negative Syndrome Scale [PANSS] score > 70). A. Least squares (LS) mean change from baseline in PANSS scores. B. Percentage of responders ($\geq 50\%$ reduction from baseline in PANSS total score). C. Proportion of subjects with clinically meaningful improvement in PANSS scores (≥ 10 point improvement). $^{*}p \leq .01$, pali ER vs placebo. †$p \leq .001$, pali ER vs placebo. ‡$p < .05$, Fisher's exact test, pali ER vs placebo. §$p < .01$, Fisher's exact test, pali ER vs placebo. LS, least squares; Pali ER, paliperidone extended-release; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

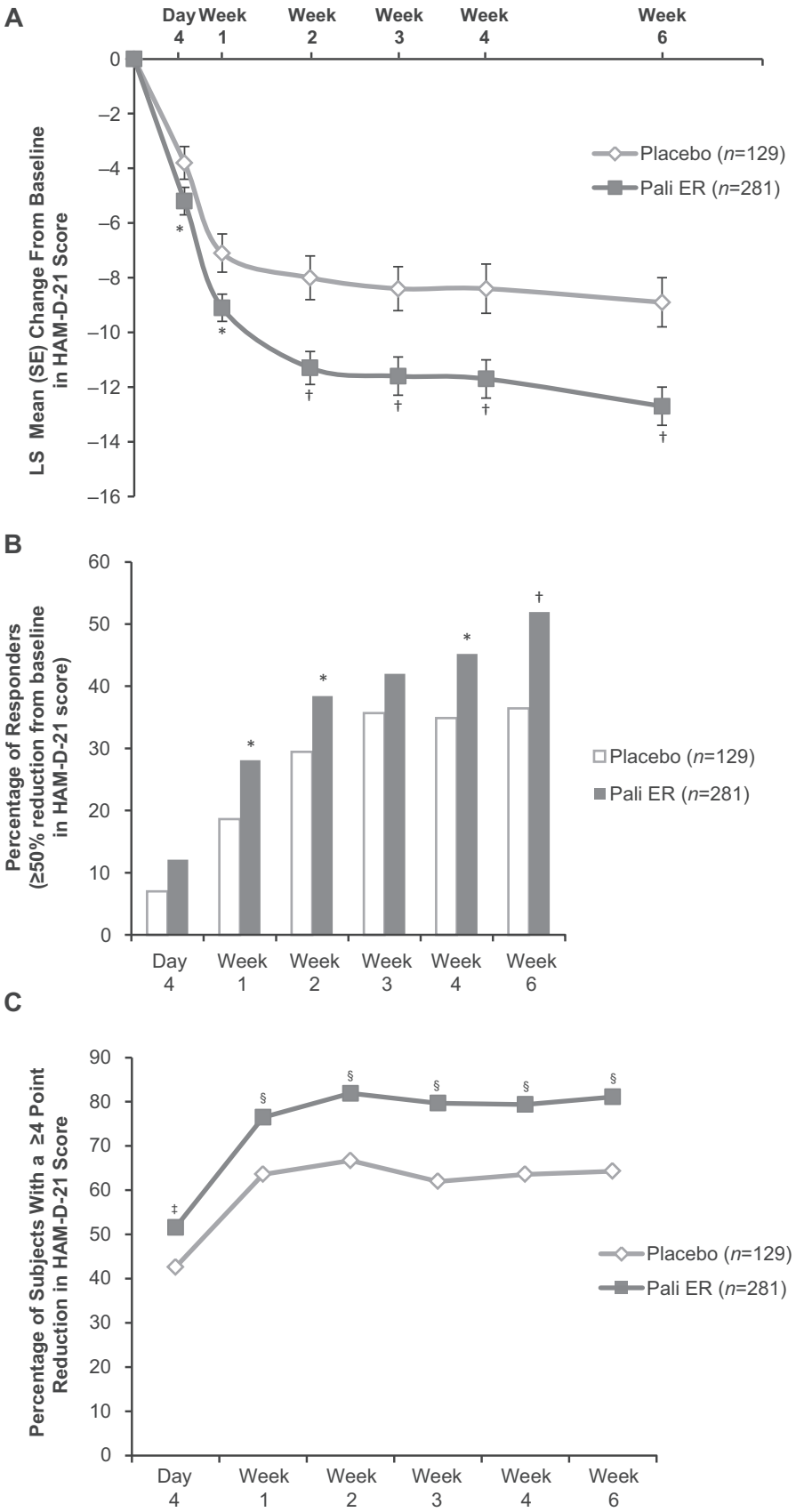

Fig. 2. Subjects with prominent depressive symptoms (HAM-D-21 $\geq$ 16). A. Least squares (LS) mean change from baseline in HAM-D-21 scores. B. Percentage of responders ($\geq$ 50% decrease from baseline in HAM-D-21 score). C. Proportion of subjects with clinically meaningful improvement in HAM-D-21 scores ($\geq$ 4-point improvement). *$p < .05$, pali ER vs placebo. †$p \leq .001$, pali ER vs placebo. ‡$p < .05$, Fisher's exact test, pali ER vs placebo. §$p < .01$, Fisher's exact test, pali ER vs placebo. HAM-D-21, Hamilton Rating Scale for Depression, 21-item version; LS, least squares; Pali ER, paliperidone extended-release; SE, standard error.

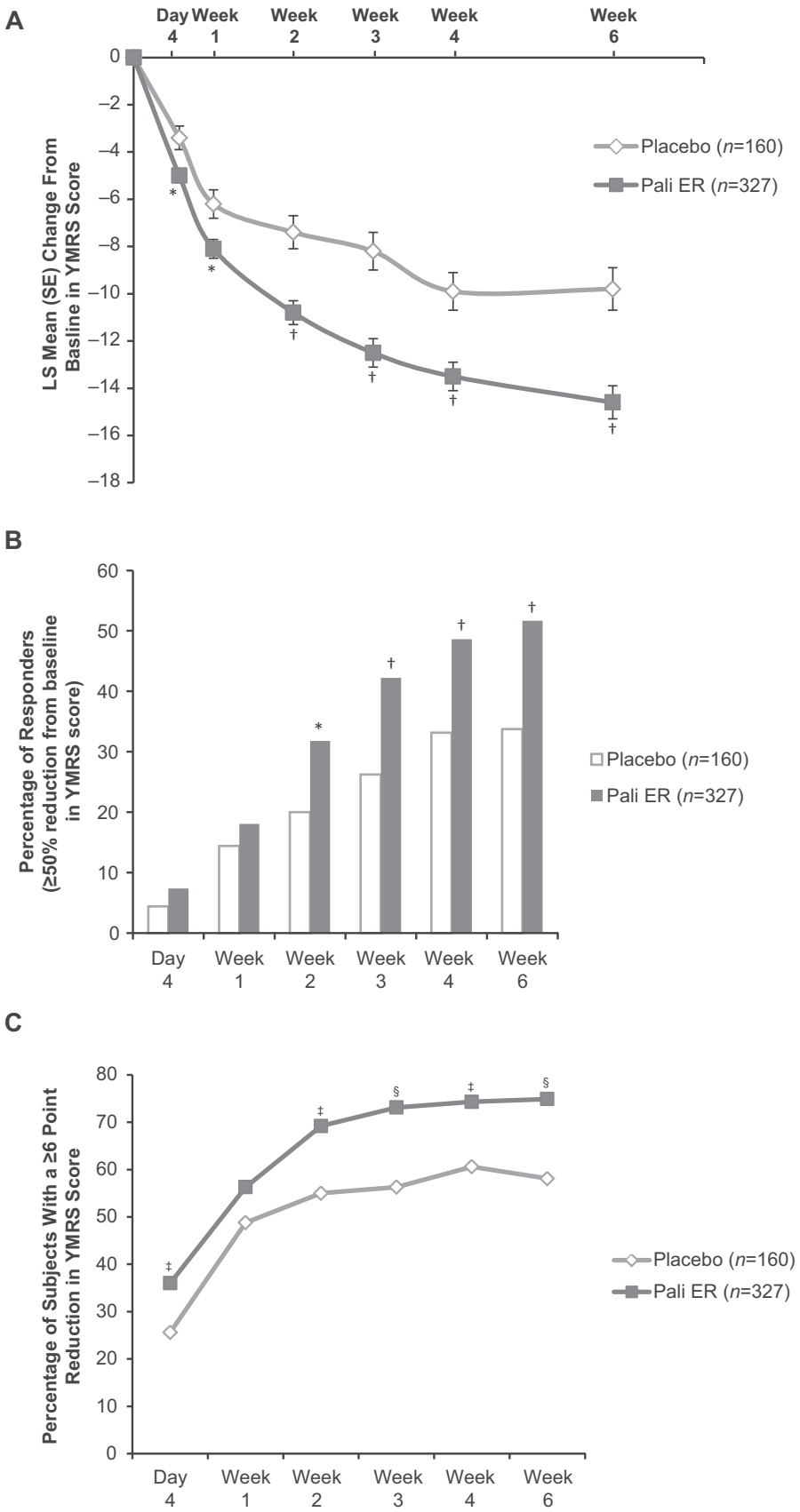

Fig. 3. Subjects with prominent manic symptoms (YMRS ≥ 16). A. Least squares (LS) mean change from baseline in YMRS scores. B. Percentage of responders (≥ 50% decrease from baseline in YMRS score). **C**. Proportion of subjects with clinically meaningful improvement in YMRS (≥ 6-point improvement). *$p \leq .01$, pali ER vs placebo. †$p < .001$, pali ER vs placebo. ‡$p < .05$, Fisher's exact test, pali ER vs placebo. §$p < .01$, Fisher's exact test, pali ER vs placebo. LS, least squares; Pali ER, paliperidone extended-release; SE, standard error; YMRS, Young Mania Rating Scale.

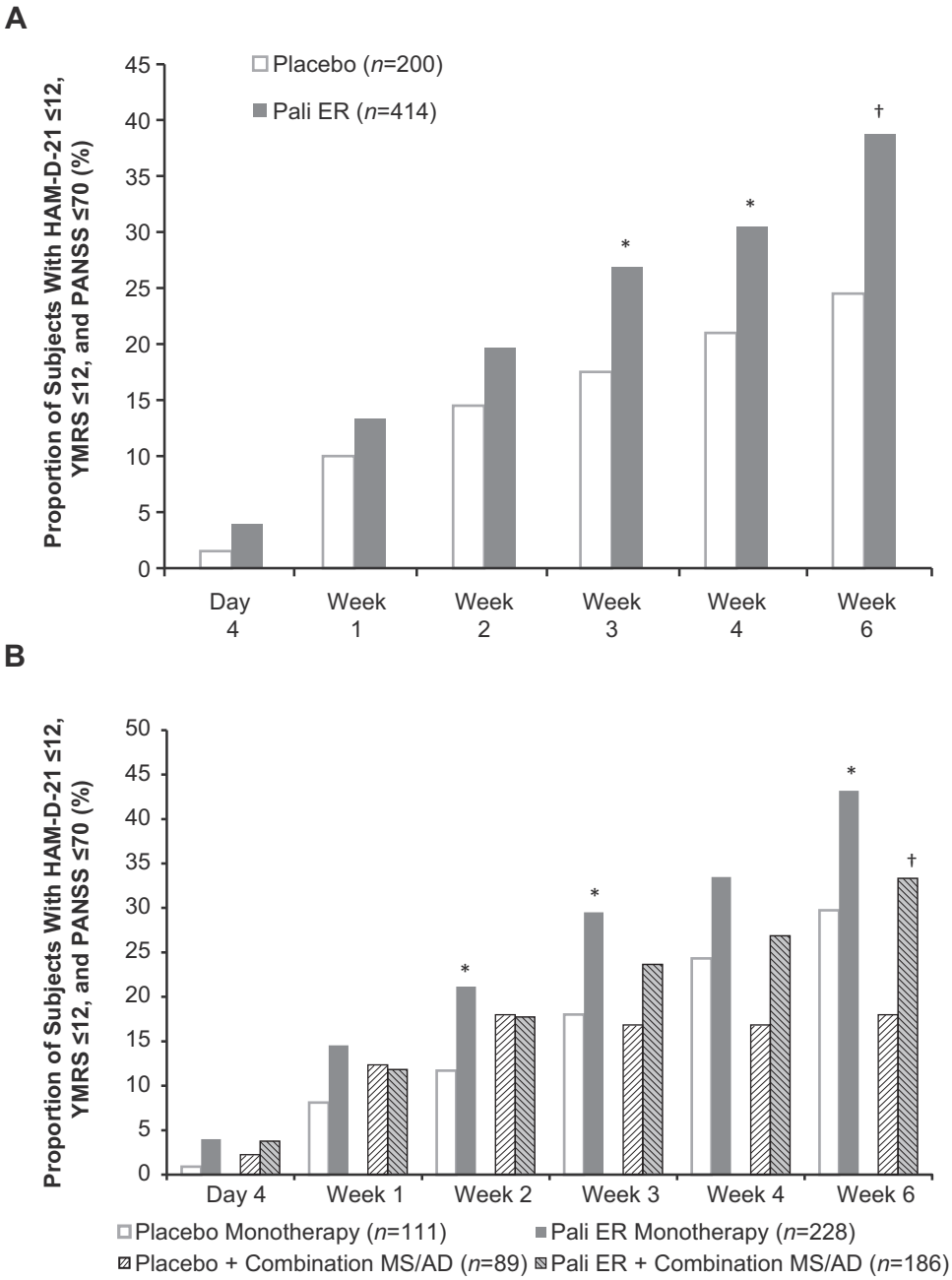

Fig. 4. Proportion of subjects at each LOCF time point who had HAM-D-21 ≤ 12, YMRS ≤ 12, and PANSS ≤ 70. A. All ITT subjects ($N=614$). B. Subjects receiving monotherapy ($n=339$), or concomitant mood stabilizers and/or antidepressants (MS/AD; $n=275$). *$p<.05$, Fisher's exact test, pali ER vs placebo. †$p<.01$, Fisher's exact test, pali ER vs placebo. AD, antidepressants; HAM-D-21, Hamilton Rating Scale for Depression, 21-item version; LOCF, last observation carried forward; MS, mood stabilizers; Pali ER, paliperidone extended-release; YMRS, Young Mania Rating Scale.

course of therapy is summarized in Fig. 2C. In this patient subgroup, mean change in YMRS and HAM-D-21 scores also significantly improved when compared with placebo from day 4 of treatment ($p \leq .01$ for all time points). Subjects with prominent manic symptoms at baseline showed clinically and statistically significant improvement in mean YMRS scores compared with placebo at day 4 of therapy. Increasing improvement was observed until week 3. Improvement plateaued from week 3 to end point ($p<.05$). Results at week 1 were not statistically significant ($p=.154$).

3.2.4. Improvement in all symptom domains

By the end of the first week of treatment, more than 13% of study subjects treated with pali ER ($n=414$) showed improvements in all baseline symptom scores (PANSS ≤ 70, HAM-D-21 ≤ 12, and YMRS ≤ 12). This number continued to increase steadily throughout the study, up to 39% by week 6, with significant ($p<.05$) improvements from week 3 onward compared with placebo (Fig. 4A). This improvement in all scores was apparent whether subjects were treated with pali ER as monotherapy or in combination with mood stabilizers and/or antidepressants (Fig. 4B)

3.3. Adverse events

Regardless of prominent baseline symptoms, approximately 69.0% of subjects treated with pali ER reported at least one

Table 2
Occurrence of treatment-emergent adverse events according to baseline symptoms (ITT population, $N=614$).

n (%)	Prominent psychotic[a] $N=597$		Prominent depressive[a] $N=411$		Prominent manic[a] $N=488$	
	Pali ER $n=402$	Placebo $n=195$	Pali ER $n=282$	Placebo $n=129$	Pali ER $n=328$	Placebo $n=160$
Number of subjects with ≥1 TEAE	277 (68.9)	115 (59.0)	194 (68.8)	80 (62.0)	226 (68.9)	93 (58.1)
Discontinuation due to AE	27 (6.7)	13 (6.7)	18 (6.4)	10 (7.8)	19 (5.8)	11 (6.9)
TEAE (MedDRA-preferred term)						
Headache	60 (14.9)	30 (15.4)	47 (16.7)	21 (16.3)	45 (13.7)	25 (15.6)
Nausea	27 (6.7)	12 (6.2)	22 (7.8)	6 (4.7)	25 (7.6)	11 (6.9)
Dyspepsia	22 (5.5)	5 (2.6)	20 (7.1)	4 (3.1)	21 (6.4)	3 (1.9)
Dizziness	26 (6.5)	12 (6.2)	19 (6.7)	10 (7.8)	21 (6.4)	8 (5.0)
Insomnia	26 (6.5)	14 (7.2)	19 (6.7)	10 (7.8)	18 (5.5)	8 (5.0)
Tremor	32 (8.0)	7 (3.6)	15 (5.3)	5 (3.9)	28 (8.5)	5 (3.1)
Akathisia	22 (5.5)	9 (4.6)	14 (5.0)	7 (5.4)	18 (5.5)	6 (3.8)
Somnolence	21 (5.2)	4 (2.1)	16 (5.7)	3 (2.3)	15 (4.6)	3 (1.9)
Hypertonia	22 (5.5)	4 (2.1)	13 (4.6)	3 (2.3)	20 (6.1)	2 (1.3)
Sedation	20 (5.0)	7 (3.6)	12 (4.3)	4 (3.1)	19 (5.8)	7 (4.4)
Dry mouth	17 (4.2)	8 (4.1)	15 (5.3)	6 (4.7)	15 (4.6)	8 (5.0)
Constipation	17 (4.2)	5 (2.6)	15 (5.3)	4 (3.1)	12 (3.7)	5 (3.1)

AE, adverse event; ITT, intent-to-treat; MedDRA, Medical Dictionary for Regulatory Activities; Pali ER, paliperidone extended-release; TEAE, treatment-emergent adverse event.

[a]The three groups are not mutually exclusive. Gray shading indicates TEAE occurring at ≥5% in the pali ER group.

treatment-emergent AE (TEAE), compared with 58.1% to 62.0% of those receiving placebo (Table 2). In subjects who received pali ER, 6.7%, 6.4%, and 5.8% in the prominent psychotic, depressive, and manic subgroups, respectively, discontinued due to an AE compared with 6.7%, 7.8%, and 6.9% of subjects who received placebo, respectively.

In the pooled database, the most frequently reported TEAEs (≥5.0% in those receiving pali ER) among subjects receiving pali ER versus placebo were headache (14.3% vs 14.9%, respectively), tremor (8.1% vs 3.5%), dizziness (6.7% vs 5.9%), insomnia (6.7% vs 6.9%), nausea (6.4% vs 5.9%), akathisia (5.5% vs 4.5%), hypertonia (5.5% vs 2.0%), dyspepsia (5.5% vs 2.5%), somnolence (5.2% vs 2.0%), and sedation (5.0% vs 3.5%) (Canuso et al., 2010c). Of these, headache, nausea, dyspepsia, dizziness, insomnia, tremor, and akathisia occurred in ≥5% of pali ER–treated subjects, regardless of prominent baseline symptom.

4. Discussion

Results from this study suggest that pali ER may be a core therapy for the treatment of all symptom domains associated with acute exacerbation of SCA. A rapid acute response was demonstrated with pali ER, which was both clinically and statistically significant within 1 week of commencing therapy. Furthermore, the treatment effect of pali ER was evident in subjects who were receiving monotherapy or adjunctive therapy with mood stabilizers and/or antidepressants. These findings are in line with the results of previous prospective studies (Canuso et al., 2010c, 2010a), which support the use of the paliperidone molecule for the acute management of SCA symptoms following relapse. Recent evidence from a long-term, randomized, double-blind, relapse-prevention study also supports the use of paliperidone as a maintenance treatment in persons with SCA (Fu et al., 2015).

In this population of subjects with SCA experiencing acute exacerbations, it is important to note that the three prominent symptom subgroups were not mutually exclusive, with most subjects exhibiting symptoms of multiple domains. This overlap of psychotic, depressive, and manic symptoms is reflective of the general SCA population and highlights the complexity of the disease. In those receiving pali ER, the initial onset of symptomatic improvement, as measured by mean changes from baseline in symptom scores, was rapid, with significant differences being evident as early as day 4 in all domains. The onset of clinically meaningful improvements in psychotic and depressive symptoms was also rapid, and significant improvements in the achievement of the more stringent end point of treatment response (≥50% reduction from baseline in symptom scores) was observed from week 2 onwards in all symptom domains. Taken together, these data add to the understanding of the onset of treatment effect on each of the symptom domains of SCA and suggest that pali ER can be used to effectively manage these symptoms following an acute exacerbation.

Pali ER has been previously evaluated in subjects with bipolar I disorder and similar symptoms (ie, acute mania or mixed episodes with or without psychotic symptoms) (Vieta et al., 2010; Berwaerts et al., 2012, 2011). Similar to our findings, the results of two placebo-controlled trials demonstrated significantly greater reductions from baseline in YMRS at week 3 (primary endpoint) for monotherapy with flexibly dosed pali ER 3–12 mg (−13.2 vs −7.4; $p<.001$) (Vieta et al., 2010) and pali ER 12 mg (−13.9 vs −9.9; $p<.01$) (Berwaerts et al., 2012) versus placebo; pali ER 3 mg and 6 mg did not separate from placebo. A 6-week adjunctive therapy study of bipolar subjects with acute mania showed no significant improvement in YMRS with flexibly dosed pali ER add-on to mood stabilizers relative to mood stabilizer monotherapy (−14.3 vs −13.2; $p=0.16$) (Berwaerts et al., 2011).

Overall, a large proportion of subjects (44.8%) were sufficiently symptomatic to enter the two studies despite receiving adjunctive therapy with mood stabilizers and/or antidepressants, indicating that these concomitant medications did not provide effective control of their symptoms. The beneficial effects of pali ER demonstrated in this study were seen regardless of whether treatment was given as monotherapy or in combination with mood stabilizers and/or antidepressants (Canuso et al., 2010c, 2010b, 2010a). The reduction in symptoms, as measured by the percentage of subjects with a composite response, occurred in a slightly higher proportion of subjects receiving pali ER monotherapy (53.5%) compared with those receiving pali ER in combination with mood stabilizers and/or antidepressants (45.2%) (Canuso et al., 2010c, 2010b, 2010a). It is possible that those subjects requiring adjunctive medication may be a more treatment-resistant

population. Indeed, the mean duration of illness in subjects requiring adjunctive medication was slightly longer than those receiving pali ER monotherapy. This is further supported by the observation that subjects in the placebo monotherapy treatment arm had a greater reduction in symptoms than those in the placebo adjunctive arm (Canuso et al., 2010c, 2010b, 2010a). The smaller treatment effect of pali ER in those receiving adjunctive medication may also reflect the partial efficacy of adjunctive therapy for some symptoms. This raises the possibility that adjunctive therapy should not be the core or backbone therapy. Rather, primary treatment might begin with the initiation of pali ER, followed by the addition of adjunctive therapy as necessary.

The overall safety and tolerability profiles of pali ER appeared similar among the different symptomatic subgroups assessed in this study. Furthermore, the pattern of TEAEs observed in these symptomatic subgroups was generally similar to that of the overall study populations (Canuso et al., 2010c, 2010a) and to that of previous short-term studies of pali ER in persons with schizophrenia (Davidson et al., 2007; Kane et al., 2007; Marder et al., 2007; Kramer et al., 2007).

There are limitations of the current analysis that should be taken into consideration. Data were analyzed from selected subjects enrolled in two randomized, controlled trials, potentially limiting the generalizability to broader groups of individuals with SCA who may be encountered in clinical practice (ie, those who were excluded from these trials). Furthermore, the substantially lower pali ER dosing in a treatment arm of one study (3 to 6 mg/day) (Canuso et al., 2010a) relative to the overall mean dose of pali ER (8.3 mg) seen across the three prominent symptom subgroups may have had an impact on the overall pali ER treatment effect in this analysis. It is also important to note that this was a post hoc analysis of pooled data from previously completed registration trials. As a result, these findings should be considered as hypothesis-generating and will require confirmation from prospective studies.

In conclusion, this post hoc analysis suggests that pali ER was associated with significant improvement relative to placebo in psychotic, depressive, and manic symptom scores. The improvements were observed as early as day 4, with greater responder rates by weeks 1 and 2 in symptomatic subjects with SCA, including those receiving adjunctive therapy with mood stabilizers and/or antidepressants. Taken together, these findings for pali ER provide additional knowledge and support for the clinical value of the paliperidone molecule for the management of SCA.

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Contributors

D.-J. Fu, C. A. Bossie, H. Patel, and L. Alphs were responsible for the design, data collection, and writing. I. Turkoz was responsible for the design, data collection, writing, and statistical analyses. All authors critically reviewed and revised the manuscript and approved the final version.

Conflicts of interest

D.-J. Fu, C. A. Bossie, and L. Alphs are employees of Janssen Scientific Affairs, LLC, and Johnson & Johnson stockholders. I. Turkoz is an employee of Janssen Research & Development, LLC, and a Johnson & Johnson stockholder. H. Patel was an employee of Janssen Scientific Affairs at the time of this analysis and is a Johnson & Johnson stockholder.

Registration

The primary studies are registered at ClinicalTrials.gov (NCT00412373 and NCT00397033).

Previous presentation

These data were presented, in part, at the 14th International Congress on Schizophrenia Research; April 21–25, 2013: Orlando, FL, USA.

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