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Social and functional outcomes with two doses of aripiprazole lauroxil vs placebo in patients with schizophrenia: a *post-hoc* analysis of a 12-week phase 3 efficacy study

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ABSTRACT

To assess the effect of the long-acting antipsychotic aripiprazole lauroxil (AL) on social and functional outcomes compared with placebo in patients with acute schizophrenia, a *post-hoc* analysis was conducted. Patients with acute schizophrenia were enrolled in a 12-week, double-blind, placebo-controlled efficacy trial, and randomized 1:1:1 to receive AL 441 mg, AL 882 mg, or placebo every 4 weeks. Changes in social functioning using the 6- and 4-item Positive and Negative Syndrome Scale (PANSS) Prosocial subscales were evaluated. The Personal and Social Performance (PSP) total score evaluated patients' global improvement. Changes from baseline were analyzed using mixed-effect models repeat measurements. PANSS Prosocial subscale scores and PSP total score improved significantly with AL vs. placebo, without any dose-related difference in magnitude of response. Significant mean ± SE improvements in 6-item PANSS Prosocial scores from baseline to Day 85 were observed for both individual active treatment groups (e.g., AL 441 mg and AL 882 mg groups) vs. placebo. There were significant changes in PSP total score from baseline to Day 85 for both AL doses vs. placebo. This *post-hoc* analysis demonstrated a significant improvement in social functioning with AL vs. placebo, as assessed by the PANSS Prosocial subscale and PSP total score.

1. Introduction

Schizophrenia is a chronic illness and is one of the leading causes of disability worldwide (Global Burden of Disease Study 2013 Collaborators, 2015). Symptoms often become evident in early adulthood and can have a significant impact on social functioning during this important developmental phase of life (Hollis, 2000). Up to two-thirds of people with schizophrenia are unable to fulfill basic social roles, and less than one-third maintain regular employment (Bellack et al., 2007), often becoming socially isolated due to difficulties in maintaining social relationships (Bellack et al., 2007). Impaired social skills may also translate into poor health outcomes (Bellack et al., 2007) due to difficulties relating to healthcare professionals. Persistent social deficits with poor social outcomes over the long term are common (Hollis, 2000). It is often reported that social and functional impairments are unresponsive to pharmacologic interventions (Guo et al., 2010), but this finding may be misconstrued as absolute lack of response rather than partial, albeit incomplete, response.

Clinical practice guidelines for schizophrenia advocate for the improvement of social functioning as part of the treatment goals for patients with schizophrenia (Hasan et al., 2012; National Institute for Health and Care Excellence, 2014). It should be noted, however, that improvements in psychotic symptoms do not always correlate with an improvement in functioning (Fleischhacker et al., 2005; San et al., 2007; Ventura et al., 2011). Improvements in cognition and social functioning are recognized as important indices of treatment success that are not always linked to acute symptoms (Huang et al., 2012).

Aripiprazole lauroxil (AL) is a long-acting formulation of a prodrug of aripiprazole approved for the treatment of schizophrenia (Alkermes, Inc., 2018). The initial pivotal study demonstrated the efficacy and safety of AL (441 mg and 882 mg doses) in a 12-week, randomized, double-blind, placebo-controlled study (Meltzer et al., 2015) and in a 1-year safety extension study (Nasrallah et al., 2018). The aim of this *post-hoc* analysis was to assess changes in social and functional domains in patients with acute schizophrenia treated with AL compared with placebo in the 12-week efficacy study. Changes were assessed

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using validated clinical scales: the Positive and Negative Syndrome Scale (PANSS) Prosocial subscales (Kay et al., 1987; Purnine et al., 2000) and the Personal and Social Performance (PSP) scale (Patrick et al., 2009).

2. Methods

This was a *post-hoc* analysis of patients with schizophrenia who enrolled in an international, multicenter, 12-week, double-blind, phase 3, placebo-controlled trial (ClinicalTrials.gov identifier: NCT01469039; European Clinical Trial Database [EudraCT] Number: 2012-00345-15) that was conducted across seven countries between December 2011 and March 2014 (Meltzer et al., 2015). The study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines by the International Conference on Harmonization, 1997. Institutional ethical review board or local ethics committee approval was obtained for each site. All patients provided informed written consent before entering the study.

2.1. Patients

Patients with acute schizophrenia ($n = 623$) were randomized in a 1:1:1 ratio to receive AL 441 mg (aripiprazole 300 mg equivalent); AL 882 mg (aripiprazole 600 mg equivalent); or placebo. Doses were administered intramuscularly once every 4 weeks for 12 weeks.

Patients assigned to one of the active AL arms also received oral aripiprazole 15 mg daily for the first 3 weeks after randomization to achieve early therapeutic exposure to aripiprazole from the combined release of AL and oral aripiprazole; placebo-arm patients received matched oral study medication.

Full details of the study design and patient eligibility criteria have been described elsewhere (Meltzer et al., 2015). Briefly, the study enrolled patients who were hospitalized for the treatment of an acute exacerbation of schizophrenia. Patients were included if they were aged 18–70 years, with a primary diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, had been an outpatient for >3 months during the year before enrolment, and had a PANSS total score of 70–120. Major exclusion criteria were the presence of another primary psychiatric diagnosis, clinically significant medical illness, history of treatment resistance, history of poor response to oral aripiprazole, being pregnant or lactating or unable or unwilling to consent (Meltzer et al., 2015).

2.2. Clinical assessments of social and functional outcomes

Social and functional outcomes were assessed using selected items from the PANSS. The PANSS Prosocial subscale, previously developed as a sensitive measure of social functioning, has been validated in patients with schizophrenia (Harvey et al., 2015; Kay et al., 1987; Loebel et al., 2004; Purnine et al., 2000). The following PANSS items were included in the 6-item Prosocial subscale: G16 [active social avoidance]; N2 [emotional withdrawal]; N4 [passive social withdrawal]; N7 [stereotyped thinking]; P3 [hallucinatory behavior]; and P6 [suspiciousness/persecution] with standard PANSS anchoring from absent (1) to extreme (7). The following 4-item PANSS Prosocial subscale was also assessed (Docherty et al., 2010): G16 [active social avoidance]; N2 [emotional withdrawal]; N4 [passive social withdrawal]; and N5 [difficulty in abstract thinking].

Other functional outcome domains were assessed using the PSP scale, a validated, clinician-administered scale that utilizes clinical interview of the patient and caregiver combined with clinical observation to measure global and personal social functioning on a 0–100 scale (Patrick et al., 2009). PSP was assessed as both change in total score and proportion of patients with categorical shifts in PSP score, defined as PSP scores of 0–30 (severe functional impairment), ≥31–50 (marked functional impairment), ≥51–70 (moderate functional impairment), and ≥71–100 (mild to no functional impairment) (Morosini et al., 2000). A 10-point shift in score was considered to be clinically significant (Nicholl et al., 2010), thus the proportion of patients with a 10-point improvement was also evaluated.

2.3. Statistical analyses

Analyses were carried out in all patients who were randomized, received at least one dose of study drug and had at least one primary efficacy assessment. The change from baseline in PANSS Prosocial scores and PSP total score were analyzed using mixed-effect models repeat measurements, and an unstructured variance-covariance matrix was used to model the within-subject variability. The model included baseline as a covariate. In addition, the analysis of PSP category shift was performed based on the last observation carried forward for imputation of missing data. Cohen's d (Cohen, 1988) was used to assess overall treatment effect sizes for the PANSS Prosocial score and PSP score. According to Cohen, 0.2 is considered a small effect size, 0.5 is a medium effect size and 0.8 is a large effect size (Cohen, 1988; Fritz et al., 2012). Additionally, for categorical outcomes, we calculated the number-needed-to-treat (NNT), dividing 1 by the risk difference.

3. Results

In total, 623 patients were enrolled into the study and randomized 1:1:1 to AL 441 mg, AL 882 mg, or placebo, of which 596 patients were included in this *post-hoc* analysis. A full CONSORT diagram and patient disposition were published in Meltzer et al. (2015).

Patient demographics and baseline social and functional outcome scores are presented in Table 1. Approximately two-thirds of patients were male, and the sample had a mean age of 39.0 years. Further details on patient demographics are available in Meltzer et al. (2015).

3.1. Positive and Negative Syndrome Scale (PANSS) Prosocial subscales

Statistically significant improvements in the 6-item PANSS Prosocial scores were observed as early as Day 8 and were maintained through to Day 85 for both doses of AL (mean ± standard error [SE] decrease from baseline to Day 85 of –6.6 ± 0.4 and –6.4 ± 0.4 points for AL 441 mg and AL 882 mg, respectively) compared with placebo (−3.4 ± 0.5 points; $p < 0.0001$ for both doses) (Fig. 1). Similar statistically significant improvements in the 4-item modified PANSS Prosocial scores were observed as early as Day 8 and maintained through Day 85 for both AL doses: the mean ± SE decrease from baseline to Day 85 was –3.1 ± 0.3 and –3.2 ± 0.2 points in patients administered AL 441 mg and AL 882 mg, respectively, compared with placebo (−1.6 ± 0.3 points; $p < 0.0001$ for both doses) (Supplemental Fig. 1). The overall treatment effect sizes for PANSS Prosocial scores with AL 441 mg or AL 882 mg compared with placebo were Cohen's $d = 0.52$ and 0.49, respectively.

3.2. Personal and Social Performance (PSP) scores

Patients who received AL for 12 weeks experienced statistically and clinically significant functional improvements, as assessed by the PSP total score (Fig. 2). Change in PSP total score was statistically significant for both doses of AL (mean ± SE improvement from baseline to Day 85 of 12.8 ± 1.1 and 14.0 ± 1.0 points for AL 441 mg and AL 882 mg, respectively) compared with placebo (5.2 ± 1.1-point improvement from baseline to Day 85; $p < 0.0001$ for both doses). Patients in the placebo group exhibited non-significant changes in functional status, as assessed by the PSP total score (Fig. 2). Clinically significant improvements in functioning were observed as early as Day 29 (mean ± SE improvement from baseline to Day 29 of 10.3 ± 1.0 and 11.4 ± 0.9 points for AL 441 mg and AL 882 mg, respectively; $p < 0.0001$ for both doses) and were maintained at Day 85 (Fig. 2). The

Table 1
Baseline patient demographic and psychiatric characteristics.

Characteristic	AL 441 mg (n = 207)	AL 882 mg (n = 208)	Placebo (n = 208)
Men, n (%)	141 (68.1)	143 (68.8)	139 (66.8)
Age, mean (SD), years	39.9 (10.1)	39.7 (11.1)	39.5 (11.9)
BMI, mean (SD), kg/m^2	27.7 (5.3)	27.3 (5.7)	27.0 (5.1)
Race, n (%)			
White	99 (47.8)	98 (47.1)	94 (45.2)
Black/African American	83 (40.1)	81 (38.9)	84 (40.4)
Asian	24 (11.6)	28 (13.5)	29 (13.9)
Other	1 (0.5)	1 (0.5)	1 (0.5)
PANSS total score, mean (SD)[a]	92.6 (10.2)	92.0 (10.8)	93.9 (11.3)
6-item PANSS Prosocial subscale score, mean (SD)[a, b]	22.8 (3.2)	22.5 (3.4)	23.0 (3.6)
Modified 4-item PANSS Prosocial subscale score, mean (SD)[a,b]	14.5 (2.7)	14.5 (3.0)	14.9 (2.9)
PSP total score, mean (SD)[a]	50.4 (12.1)	50.9 (12.5)	48.6 (12.8)
PSP total score, n (%)[a,c,d]			
1–30	7 (3.6)	10 (4.9)	16 (8.2)
31–50	102 (52.3)	104 (51.2)	101 (51.8)
51–70	78 (40.0)	75 (37.0)	68 (34.9)
71–100	8 (4.1)	14 (6.9)	10 (5.1)
CGI-S score, mean (SD)[a]	4.9 (0.6)	4.9 (0.6)	4.9 (0.6)

AL, aripiprazole lauroxil; BMI, body mass index; CGI-S, Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; SD, standard deviation.

[a] Patients in the *post-hoc* analysis population for AL 441 mg, n = 196; for AL 882 mg, n = 204; for placebo, n = 196.

[b] Each PANSS item is rated from absent (1) to extreme (7) (Purnine et al., 2000); the 6-item PANSS Prosocial subscale score range is 6–42 and 4-item PANSS Prosocial subscale score range is 4–28.

[c] Measurement for one patient missing from each study group.

[d] PSP scores on a scale of 0–100: 0–30 = severe functional impairment, ≥31–50 = marked functional impairment, ≥51–70 = moderate functional impairment, and ≥71–100 = mild to no functional impairment (Morosini et al., 2000).

overall treatment effect sizes for PSP total score with AL441 mg or AL 882 mg compared with placebo were Cohen's d = 0.51 and 0.59, respectively.

A significantly greater proportion of patients treated with AL exhibited a clinically significant improvement in functioning, as measured by a ≥ 10-point shift from baseline in PSP score, compared with placebo. Overall, by Day 85, 57.2% and 60.5% of patients in the AL 441 mg (n = 103/180) and AL 882 mg groups (n = 112/185), respectively, compared with 30.7% (n = 55/179) of patients in the placebo group, experienced a clinically significant improvement in functioning, translating into an NNT = 3.8 for AL 441 mg and NNT = 3.4 for AL 882 mg. A significant difference in the proportion of patients demonstrating a ≥ 10-point shift in PSP total score was observed as early as Day 8.

Functional status, as assessed by PSP total score changes by category, is shown in Fig. 3. Patients who received AL 441 mg showed an overall trend in change from marked/moderate to mild/moderate functional impairment. Patients who received AL 882 mg showed a trend in change from severe/marked to moderate/mild functional impairment. Fewer patients treated with AL 882 mg were severely functionally impaired at Day 85 compared with those treated with AL 441 mg (0.5% vs 4.4%, respectively), with the highest proportion in the placebo group (8.4%). Patients who received placebo showed a trend toward a change from marked/moderate to moderate/mild functional impairment.

3.3. Adverse events

Discontinuation for adverse effects was low with both doses of AL (AL 441 mg: 6.8%, AL 882 mg: 2.9% and placebo: 17.9% of patients) (Meltzer et al., 2015). AL had an adverse-event profile that was consistent with that of oral aripiprazole (Meltzer et al., 2015). The frequency of injection-site reactions was low and predominantly described as injection-site pain associated with the first injection in the gluteal muscle (Meltzer et al., 2015). Full details of the adverse events observed have been provided in Meltzer et al. (2015).

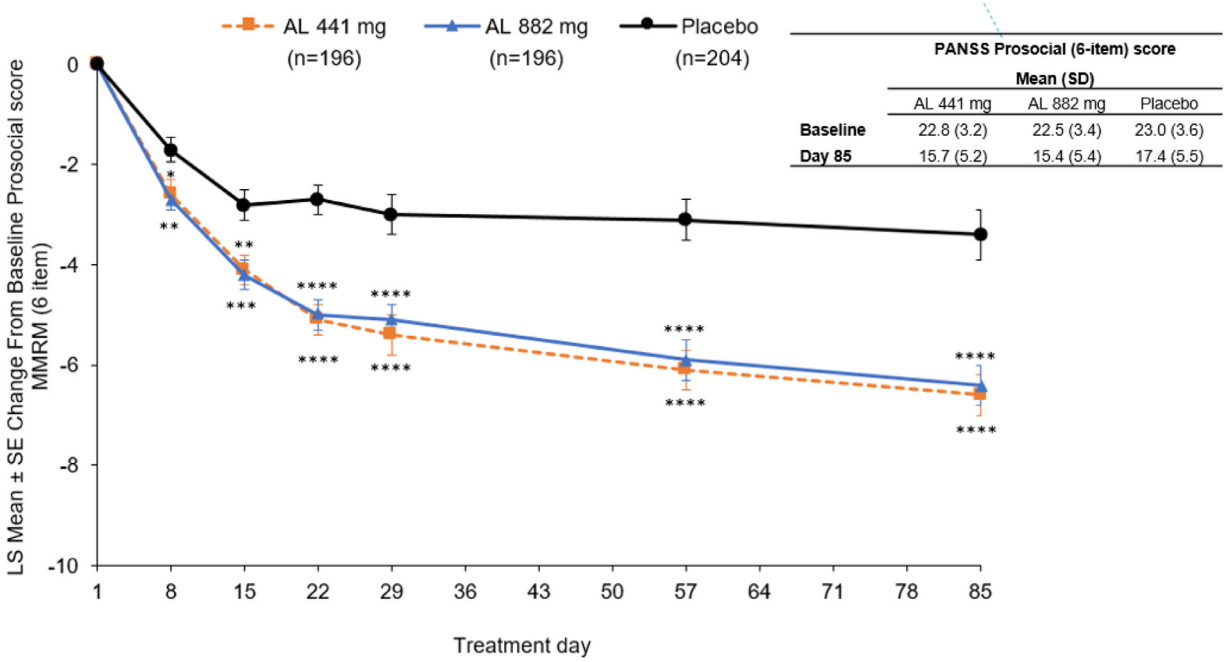

Fig. 1. Change in PANSS Prosocial Subscale (6-item) Scores over time. *p < 0.01; **p < 0.005; ***p < 0.001; ****p < 0.0001, p values vs placebo.
Each PANSS item is rated from absent (1) to extreme (7) (Purnine et al., 2000), such that the score range is 6–42. AL, aripiprazole lauroxil; LS, least squares; MMRM, mixed-effect model repeat measurements; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; SE, standard error.

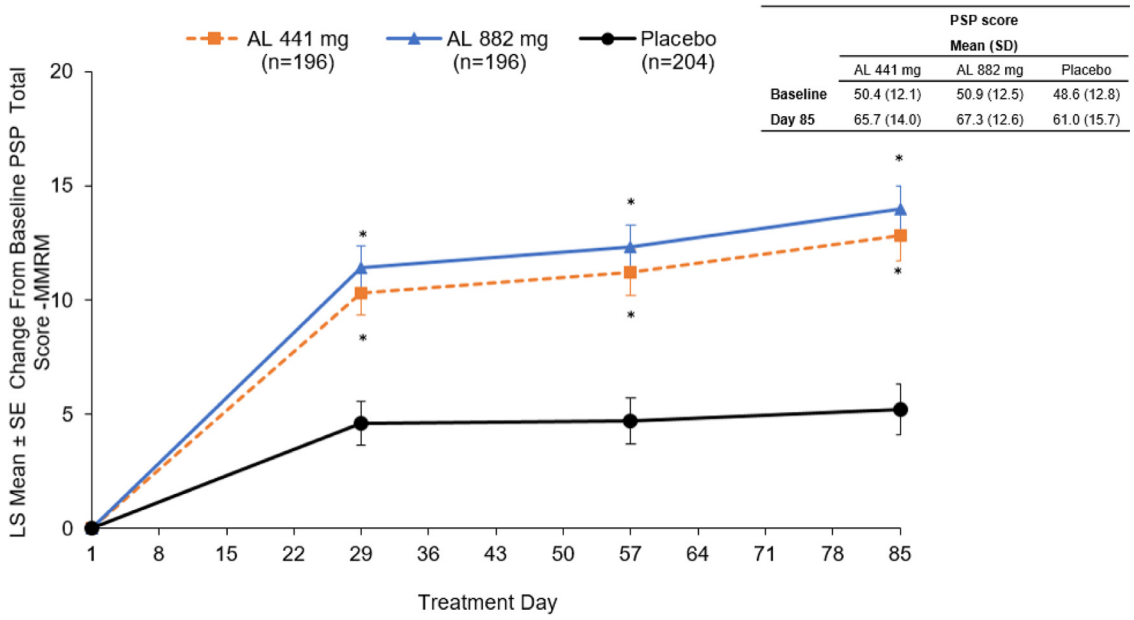

Fig. 2. Change from baseline to Day 85 in PSP total score over time. *$p < 0.0001$, p-values vs placebo. PSP scores on a scale of 0–100: 0–30 = severe functional impairment, ≥31–50 = marked functional impairment, ≥51–70 = moderate functional impairment, and ≥71–100 = mild to no functional impairment (Morosini et al., 2000). AL, aripiprazole lauroxil; LS, least squares; MMRM, mixed-effect model repeat measurements; PSP, Personal and Social Performance; SD, standard deviation; SE, standard error.

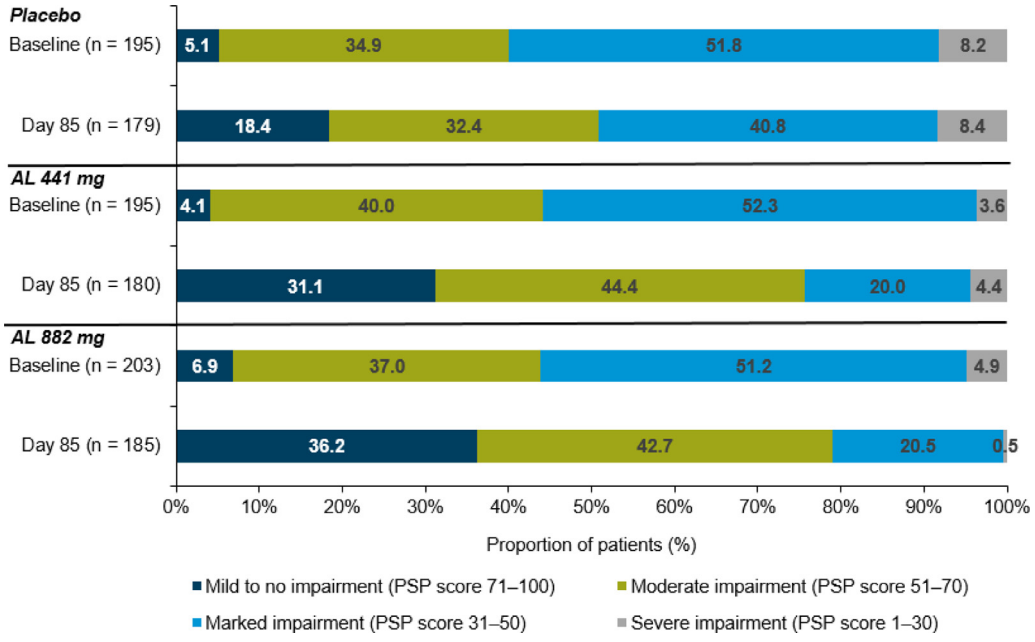

Fig. 3. Frequency of PSP categories at baseline and at Day 85
AL, aripiprazole lauroxil; PSP, Personal and Social Performance.

4. Discussion

In this *post-hoc* analysis, patients with acute schizophrenia who received AL had significantly improved PANSS Prosocial and modified PANSS Prosocial scores compared with patients who received placebo as early as Day 8, and the improvements were maintained throughout the 12-week duration of the study. Although this study was not designed as an evaluation of the shorter 4-item modified Prosocial scale, it appears that the 4-item scale was adequately sensitive to change over time, as well as active drug/placebo differences. The PSP scores showed a similar trajectory of improvement at Day 8 until the end of the 12-week study. A significantly greater proportion of patients administered AL achieved a clinically significant 10-point improvement in PSP score compared with placebo (NNT = 3.4 to 3.8), and more patients experienced a shift to categories of improved social functioning.

Measurement of social functioning in patients with schizophrenia is a complex topic due to the multifaceted nature of the condition, and thus challenges with the use of assessment scales must be acknowledged (Brissos et al., 2011). In fact, while a wide selection of assessment instruments are available, there is a lack of consensus regarding the definition and measurement of social functioning in schizophrenia (Figueira and Brissos, 2011). The present *post-hoc* analysis utilizes data from the PSP scale, a validated, clinician-administered scale that measures global and personal social functioning (Patrick et al., 2009), in

addition to the PANSS Prosocial and modified Prosocial subscales, reflecting emotional withdrawal and a lack of social interaction, with the aim of covering a broad range of aspects of social functioning. However, it has previously been acknowledged that functional recovery in schizophrenia is impacted by a range of factors, and the relationship of an improvement in a PANSS-derived measure of social functioning on overall functional recovery is not fully understood (Docherty et al., 2010).

Social and functional impairments in patients with schizophrenia are difficult to treat and may not correlate with improvements in clinical symptoms (Fleischhacker et al., 2005; Hasan et al., 2012; San et al., 2007; Ventura et al., 2015); however, this study demonstrated that the overall efficacy of AL (Meltzer et al., 2015) translated into improved social functioning for patients with acute schizophrenia. Treatment with AL has further been reported to reduce agitation and hostility (Citrome et al., 2016). Improvements in social function have also been reported with oral aripiprazole (Docherty et al., 2010). Enhancing social functioning for patients with acute schizophrenia may assist in maintaining social relationships, reducing isolation, and improving employment opportunities (Bellack et al., 2007).

Other studies have also demonstrated improvements in PSP with the long-acting formulation of aripiprazole. In two long-term studies (38 and 52 weeks) investigating the treatment of patients with acute schizophrenia, aripiprazole long-acting formulation was reported to significantly reduce PSP scores (Fleischhacker et al., 2014). Notably, patients in the present study had lower mean baseline PSP total scores (50 points; indicating marked to severe functional impairment) compared with >60 (indicating moderate functional impairment) in the aripiprazole long-acting injection study (Fleischhacker et al., 2014). Interestingly, although increased PSP scores were observed during the dose-stabilization phase (12 weeks), a further reduction in PSP score was reported during the double-blind phase (52 weeks) (Fleischhacker et al., 2014). The results of the present study are consistent with the improvement in the PSP social subdomains with aripiprazole long-acting injection (Fleischhacker et al., 2014).

The improvement in PSP total score for AL is similar to that reported in acute patients treated with paliperidone palmitate. In a 6-month, open-label study of monthly paliperidone palmitate in patients with acute schizophrenia, previously unsuccessfully treated with oral antipsychotics, PSP total scores increased by ≥10 points over the study period (Hargarter et al., 2015). In the 28-week QUALIFY study, patients with stable schizophrenia receiving once-monthly long-acting aripiprazole reported greater improvements in functional and quality-of-life outcomes, and significantly greater improvements in social initiative, than patients treated with paliperidone palmitate (Potkin et al., 2017).

A limitation of this *post-hoc* study was the short 12-week duration of the parent study (Meltzer et al., 2015). Moreover, the use of oral aripiprazole supplementation for the first 21 days provides the therapeutic concentrations that account for the early significant improvements (Day 8) in the PANSS Prosocial subscales scores. Since patients had an acute exacerbation at baseline, some of the social and functional improvements could have been secondary to an improvement in positive symptoms. However, research has indicated that social and functional impairments in schizophrenia patients may not correlate that closely with clinical symptom improvements (Fleischhacker et al., 2005; Hasan et al., 2012; San et al., 2007; Ventura et al., 2015). Furthermore, achieving the full degree of functional improvement may take longer than 12 weeks and likely differs based on the treatment setting and whether psychosocial interventions are paired with pharmacological treatments. Nevertheless, although patients had to be hospitalized at baseline, they could be discharged and treated as outpatients as early as 2 weeks after the first injection, and based on investigator judgment. Another limitation was that at some sites, the same rater completed the PANSS and PSP, while at others, it could have been completed by different raters. Additionally, the use of subscales of the PANSS to define social functioning is a limitation, because a limited number of subdomains have been assessed in this study and they have not been independently validated in patients with schizophrenia. However, the broad use of PANSS in clinical studies in the literature suggests that these findings can be compared in the future with any *post-hoc* analysis that may be conducted using data from other longer-term studies investigating the impact of treatment on social functioning. Furthermore, it has been suggested that exploratory analysis of supportive efficacy endpoints may provide more intuitive clinical information than absolute point changes on clinical rating scales on the relative efficacy of AL compared with placebo (Citrome et al., 2017). As post-hoc analyses are limited in their application and may be subject to an increased risk of bias, long-term, prospective studies focusing on social functioning are required to confirm the present outcome.

In conclusion, patients with acute schizophrenia who received 12 weeks of treatment with AL showed significant improvements in social functioning translating into a medium effect size compared with placebo, as assessed by the PANSS Prosocial subscales and the PSP scores.

Contributions

All authors were involved in the analysis and interpretation of the data, and writing the manuscript. All authors read and approved the final manuscript.

Role of the funding source

The study sponsor, Alkermes, Inc., was involved in the design, collection, and analysis of the data. Interpretation of the results was by the authors.

Declaration of interest

Arielle D. Stanford, Amy Claxton, Yangchun Du, Peter J. Weiden are employees of Alkermes, Inc.

Dr Correll has been a consultant and/or advisor to, or has received honoraria from, Alkermes, Allergan, Angelini, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medavante, Medscape, Merck, Neurocrine, Otsuka, Pfizer, ROVI, Servier, Sunovion, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Pfizer, Roche, and ROVI. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.02.021.

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