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Long-term effectiveness of aripiprazole once-monthly for schizophrenia is maintained in the QUALIFY extension study☆☆☆

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ABSTRACT

Objective: To evaluate long-term safety and effectiveness of continued treatment with aripiprazole once-monthly 400 mg (AOM 400) in patients with schizophrenia.

Methods: Patients who completed the QUALIFY study (NCT01795547) in the AOM 400 arm were eligible for 6 additional once-monthly injections of AOM 400 during an open-label, 24-week extension (NCT01959035). Safety data were collected at each visit. Effectiveness measures included change from baseline in health-related quality of life and functioning on the Heinrichs-Carpenter Quality of Life scale (QLS) and Clinical Global Impression – Severity (CGI-S) scale.

Results: Of the 88 patients enrolled, 77 (88%) completed the extension study. Most common treatment-emergent adverse events (incidence $\geq 2\%$) were weight increased (6/88, 7%), toothache (3/88, 3%) and headache (3/88, 3%). Effectiveness was maintained during the extension study, with small but continued improvements from baseline: the least squares mean (LSM) change (95% CI) from baseline to week 24 was 2.32 (–1.21 to 5.85) for the QLS total score and –0.10 (–0.26 to 0.06) for the CGI-S score. The aggregated LSM change (95% CI) from baseline of the lead-in study to week 24 of the extension study was 11.54 (7.45 to 15.64) for the QLS total score and –0.98 (–1.18 to –0.79) for the CGI-S score.

Conclusions: AOM 400 was well tolerated in patients continuing AOM treatment during the extension phase of the QUALIFY study. Robust and clinically meaningful improvements in health-related quality of life and functioning were maintained, further supporting the long-term clinical benefits of AOM 400 for the treatment of patients with schizophrenia.

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Abbreviations: AE, adverse event; APTS, all-patients-treated set; AOM 400, aripiprazole once-monthly 400 mg; CGI-S, Clinical Global Impressions-Severity; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; EPS, extrapyramidal symptoms; FAS, full analysis set; LAI, long-acting injectable; LSM, least squares mean; MMRM, mixed model for repeated measures; PP, paliperidone palmitate; QUALIFY, QUALity of Life with AbiliFY Maintena[®]; QLS, Quality of Life Scale; QoL, quality of life; TEAE, treatment-emergent adverse event.

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1. Introduction

Schizophrenia is a chronic, heterogeneous, and progressively disabling mental illness characterized by frequent relapses (Falkai et al., 2006). Relapse results in further deterioration of the illness and carries serious psychosocial implications (Emsley et al., 2013). Several studies have identified factors associated with the risk of relapse (Ascher-Svanum et al., 2010; Haddad et al., 2014; Novick et al., 2009; Olivares et al., 2013). Among these risk factors, nonadherence to medication remains a significant challenge in the management of patients with schizophrenia (Lindenmayer et al., 2009; Velligan et al., 2009). Long-acting injectable (LAI) formulations of antipsychotics have been shown to reduce relapse rates in randomized as well as naturalistic studies and have the potential to improve treatment adherence by simplifying the dosing regimen (Brisso et al., 2014; Kane et al., 2013; Kaplan et al., 2013; Kishimoto et al., 2013). Multiple randomized controlled trials have demonstrated the safety and efficacy of the atypical antipsychotic LAI aripiprazole once-monthly 400 mg (AOM 400) for the treatment of schizophrenia (Fleischhacker et al., 2014; Ishigooka et al., 2015; Kane et al., 2012; Kane et al., 2014). Continued tolerability, symptom control, and low risk of relapse was further shown in a 52-week open-label maintenance study (Peters-Strickland et al., 2015).

While relapse prevention has been the major goal of schizophrenia treatment, increasing attention is being focused on a more comprehensive approach, which includes patient functioning and quality of life (QoL) as treatment outcome measures (Hasan et al., 2013; Lehman et al., 2004; Novick et al., 2009; Pinna et al., 2013; Valencia et al., 2015). QUALity of Life with AbiliFY Maintena[®] (QUALIFY) was a head-to-head study that compared the effects of 2 LAIs: AOM 400, a dopamine D₂ receptor and serotonin 5HT-_{1A} receptor partial agonist, and paliperidone palmitate (PP), a dopamine D₂ receptor antagonist, on health-related QoL and functioning as the primary outcome. Results of the primary analysis of the QUALIFY lead-in study showed that AOM 400 provided non-inferior and superior improvement in scores on the clinician-rated Heinrichs-Carpenter Quality of Life Scale (QLS) compared with PP (mean change from baseline to week 28: 7.47 ± 1.53 vs 2.80 ± 1.62). In addition, AOM 400 treatment provided greater improvements than PP on the Clinical Global Impression-Severity (CGI-S) scale (Naber et al., 2015).

The open-label extension study reported here was designed to obtain information on the safety, tolerability, and effectiveness of continued AOM 400 treatment in patients who completed the lead-in QUALIFY study. When aggregated to the data from QUALIFY study, this study provides nearly 1 year of data on the safety and effectiveness of AOM 400 for the long-term treatment of schizophrenia.

2. Methods

2.1. Study design

This was an interventional, multinational, open-label, 28-week extension study (NCT01959035) in patients with schizophrenia who completed the lead-in QUALIFY study (NCT01795547), having received treatment with AOM 400 for 24 weeks. The details of the QUALIFY study have been published previously (Naber et al., 2015). The extension study consisted of a baseline visit, which was the completion visit at the end of the QUALIFY study; a 24-week open-label period, where patients received 6 AOM 400 injections; and a 4-week safety follow-up period after completion of or withdrawal from the study. Use of antidepressants, mood stabilizers, and benzodiazepines was allowed during the study. The starting dose of AOM in the extension study was the same as the last dose received in the lead-in QUALIFY study, and dose adjustments to 300 mg or back to 400 mg were permitted per investigators' judgment.

The study was conducted between October 2013 and March 2015 at 38 sites in 9 countries, in accordance with the principles of Good Clinical

Practice and the Declaration of Helsinki. The protocol was approved by the appropriate ethics committees.

2.2. Patients

Outpatients aged 18 to 60 years, diagnosed with schizophrenia per DSM-IV-TR (*Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision*) criteria, who completed AOM 400 treatment in QUALIFY, and who were judged by the investigator to potentially benefit from continued treatment with AOM 400 were offered enrollment in the extension study. Eligibility criteria for the lead-in QUALIFY study have been previously described (Naber et al., 2015). Patients diagnosed with clinically significant unstable illness during QUALIFY and those at significant risk of suicide were excluded from the extension study. Patients would also have been excluded if they had moderate or severe, ongoing treatment-related adverse events (AEs) in the lead-in study. Only 2 patients had ongoing AEs at the end of QUALIFY study, both of which were mild. Written consent was obtained from all patients or their legal representatives before study participation. Consistent with International Council on Harmonisation (ICH) guidelines, patients were reimbursed for documented reasonable costs associated with the study in accordance with local regulation and policies, as reviewed and approved by the ethics committee or institutional review board at each site.

2.3. Assessments

The primary endpoint was safety. Safety assessments included AEs, clinical safety laboratory tests, vital signs, weight/body mass index, and electrocardiogram (ECG). AEs were coded according to the Medical Dictionary for Regulatory Activities, version 16.1. AEs starting or worsening after baseline of the extension study were considered treatment-emergent AEs (TEAEs). Prolactin-related symptoms, extrapyramidal symptoms (EPS), and injection-site reactions were monitored. Suicidality was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2009). Secondary effectiveness measures included change from baseline to week 24 on the QLS (Heinrichs et al., 1984) and CGI-S scales (Guy, 1976). QLS is a semi-structured interview for assessing intrapsychic, social, and negative symptoms and their consequences for functioning in schizophrenia (Heinrichs et al., 1984). QLS total score ranges from 0 to 126; change of ≥5.3 points is considered clinically relevant (Falissard et al., 2016). CGI-S is a 7-point scale measuring the clinician's impression of a patient's illness severity with ratings from 1 (normal-not at all ill) to 7 (extremely ill). During the lead-in study, QLS raters were blinded to treatment assignment, CGI-S raters were not; in the extension study, all raters were aware of treatment. Treatment effectiveness was assessed at baseline and weeks 12 and 24. Safety was evaluated at all visits.

2.4. Statistical analysis

Safety and effectiveness analyses were conducted on the all-patients-treated set, which included patients receiving at least 1 dose of AOM 400 in the extension study (n = 88). Additional post hoc analyses were performed using data for the 77 patients who completed the extension study. Descriptive statistics for safety variables were summarized by visit and for the last assessment. C-SSRS scores were summarized by visit for patients with at least 1 post-baseline assessment. Missing C-SSRS scores were not imputed. Change from baseline in QLS total score and CGI-S score was calculated using a mixed model for repeated measures (MMRM). All statistical analyses were performed using Win SAS[®], version 9.3 or later.

3. Results

3.1. Patient disposition

Of the 100 patients in the AOM 400 treatment group who completed the lead-in QUALIFY study, 88 (88%) chose to enroll in the extension phase. The mean age of the study population was 43 years and the mean duration of schizophrenia at the time of study entry was 13.4 years (Table 1). Prior to enrollment in the QUALIFY study, 83 patients had received antipsychotic treatment of any type for a mean (SD) duration of 3.8 (4.7) years. Three patients were treated with clozapine and 21 had received LAIs for a mean (SD) duration of 3.0 (4.2) years. Of the enrolled patients, 77 (88%) completed and 11 (13%) discontinued the extension study (Fig. 1). The most frequent reasons for withdrawal from the study were AEs ($n = 5$) and withdrawal of consent ($n = 4$). The demographic and baseline clinical characteristics (from baseline of the lead-in QUALIFY study) were similar between the patients who entered the extension study ($n = 88$) and the full sample of patients who completed the extension study ($n = 77$). The mean QLS total and CGI-S scores at baseline of the QUALIFY lead-in study were also comparable between the full sample and completers (67.0 vs 66.7 and 4.10 vs 4.12, respectively).

The maximum duration of exposure to AOM 400 was 24 weeks in the extension study and 48 weeks in both the lead-in and extension studies combined. At baseline of the extension study, most patients (88%) received the 400 mg dose. For 2 patients, a dose reduction was required from 400 mg at baseline to 300 mg at week 4. A total of 7 patients (8%) started new use of benzodiazepines or anticholinergics in the extension study. Three patients were hospitalized during the study, 2 for psychiatric and 1 for non-psychiatric reasons.

3.2. Safety and tolerability

The proportion of patients with TEAEs during the extension study was 47% (41/88); these included weight increased (7%), toothache (3%), and headache (3%) (Table 2). The majority of TEAEs were mild or moderate in severity. Only 1 patient had 2 TEAEs that were severe (non-cardiac chest pain and gastroesophageal reflux disease), both judged as not drug-related. The incidences of serious AEs and TEAEs leading to withdrawal were 3% and 5%, respectively. The only TEAE that led to withdrawal in ≥ 2 patients was weight increased ($n = 2$). One additional patient withdrew because of an AE of weight increased that began in the lead-in phase and continued into the extension study (i.e., not considered a TEAE in the extension). Worsening of schizophrenia and alcoholism led to withdrawal in 1 patient each. No deaths were reported during the study.

Table 1
Patient demographics and baseline disease characteristics^a.

Characteristic	AOM 400 (N = 88)
Age, years, mean \pm SD	43.4 \pm 10.9
Sex, n (%)	
Female	36 (40.9)
Male	52 (59.1)
Weight, kg, mean \pm SD	85.0 \pm 16.9
BMI, kg/m ² , mean \pm SD	29.1 \pm 5.6
Duration of schizophrenia, y, mean \pm SD	13.4 (10.7)
Race, n (%)	
White	70 (79.5)
Black or African American	17 (19.3)
Asian	1 (1.1)
CGI-S score, mean \pm SD	3.2 \pm 0.8
QLS total score, mean \pm SD	76.3 \pm 22.3

AOM = aripiprazole once-monthly 400 mg; BMI = body mass index; CGI-S = Clinical Global Impression-Severity scale; QLS = Heinrichs-Carpenter Quality of Life Scale.

^a Refers to baseline of the QUALIFY lead-in study. CGI-S and QLS scores were obtained at baseline of the extension study.

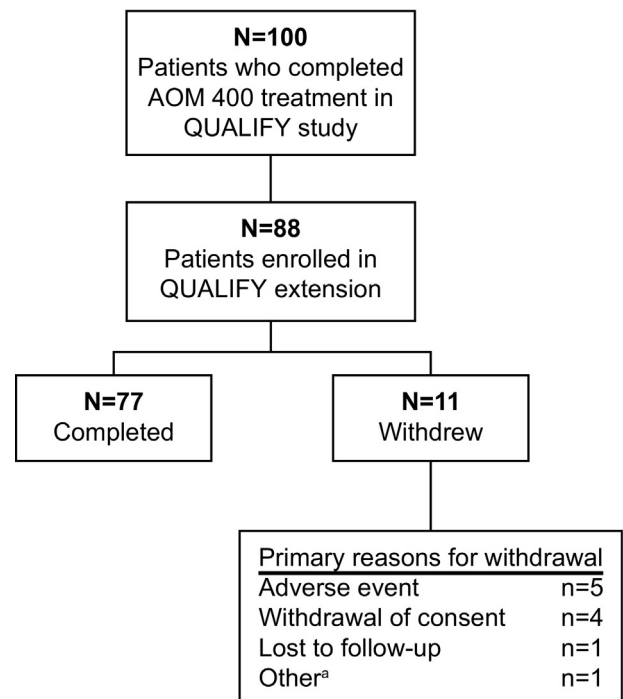


Fig. 1. Patient disposition. ^aOne patient withdrew without a primary reason being recorded. AOM 400 = aripiprazole once-monthly 400 mg.

In the extension study, 32 patients (36%) reported TEAEs for the first time, i.e., these AEs were not reported by the same patients in the lead-in study. Among the first-time events, anxiety, dizziness, hypercholesterolemia, and nasopharyngitis were reported in 2 patients (2%) each (Table 2); all other first-time events were reported by 1 patient each. The proportion of patients experiencing TEAEs was similar between those who completed the study (34/77, 44.2%) and the total study population (41/88, 46.6%).

No clinically relevant changes in clinical safety laboratory tests, vital signs, or ECG values were seen. From baseline of the extension study, 6 patients (7%) had potentially clinically significant weight gain ($\geq 7\%$ increase from baseline). None of the patients in the extension study had

Table 2
TEAEs in the QUALIFY extension study.

	AOM 400 (n = 88) n (%)
Patients with any TEAE	41 (47)
Patients with any SAE	3 (3)
Deaths	0 (0)
TEAEs occurring at an incidence of $\geq 2\%$	
Weight increased	6 (7)
Headache	3 (3)
Toothache	3 (3)
Schizophrenia	2 (2)
Anxiety	2 (2)
Asthenia	2 (2)
Hypercholesterolemia ^a	2 (2)
Nasopharyngitis	2 (2)
Dizziness	2 (2)
All SAEs	
Alcoholism	1 (1)
Dysphoria	1 (1)
Gastroesophageal reflux disease	1 (1)

AOM 400 = aripiprazole once-monthly 400 mg; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

^a Cholesterol levels (mmol/L [mg/dL]) for 2 patients at baseline of the lead-in QUALIFY study, baseline of the extension study, and week 24 of the extension study were 6.8 [263], 7.7 [298], and 6.7 [259] for one patient, and 6.8 [263], 5.9 [228], and 4.6 [178] for the other patient, respectively.

prolactin-related symptoms. The incidence of injection site reactions was low (2%, $n = 2$). First-time TEAEs related to EPS were reported in 2 patients; 1 event (tremor) was mild and considered related to AOM 400, and 1 (psychomotor hyperactivity) was moderate and considered not related to AOM 400. No patient in the study had suicidal behavior defined as C-SSRS score from 6 to 10; 1 patient (1%) had suicidal ideation on 3 occasions.

3.3. Effectiveness

Patients in the extension study showed sustained improvement in QLS total scores (Fig. 2). Mean (SD) QLS total score at baseline was 76.3 (22.3). At week 24, the least squares mean (LSM) change in the QLS total score was 2.3 (95% CI, -1.2 to 5.9). Exploratory analysis showed that the aggregated LSM change from the baseline of the lead-in study to week 24 of the extension study was 11.5 (95% CI, 7.5 to 15.6). Similarly, improvements were observed in the CGI-S scores (Fig. 3). At entry into the extension study, the mean (SD) CGI-S score was 3.2 (0.8). The LSM change from baseline in CGI-S score was -0.1 point (95% CI, -0.3 to 0.1). The aggregated LSM change in CGI-S scores from baseline of QUALIFY study to week 24 of the extension study was -0.98 (95% CI, -1.2 to -0.8).

Findings from a post hoc analysis of the 77 patients who completed the extension study were comparable with the total study population. In the extension study completers, the mean change from baseline in QUALIFY to week 24 of the extension study was 12.8 (95% CI, 8.5 to 17.2) in QLS total score (Fig. 2) and -1.0 (95% CI, -1.2 to -0.8) in the CGI-S score (Fig. 3).

4. Discussion

During the 28-week extension of the QUALIFY study, patients continuing treatment with AOM 400 demonstrated sustained improvement in QoL and functioning as assessed by the QLS and CGI-S scales. Initial improvements observed in the lead-in QUALIFY study were maintained. Combined with the findings from the QUALIFY study, these extension study data provide information on treatment with AOM 400 for nearly 1 year. As expected when patients choose to continue a treatment, the safety and tolerability results were acceptable during the extension, and most notable was the high completion rate (88%).

Long-term maintenance treatment is recommended to prevent symptomatic relapse and promote functional improvement in patients with schizophrenia (Hasan et al., 2013). When aggregated to the results

of the lead-in QUALIFY study, wherein a mean change of 7.47 ± 1.53 in QLS total score was observed with AOM 400, a clinically meaningful change (Falissard et al., 2016) of 11 points in the QLS total score, more than double the minimal clinically important difference (MCID), was noted with up to 48 weeks of treatment with AOM 400. This highlights the importance of continuing treatment with AOM 400 to maintain or achieve additional functional improvements. The improvements in QLS observed during the QUALIFY study along with the high enrollment and completion rate in the extension study also suggest that improvements in QoL allow the patients to stay on their treatment longer.

Few studies in the existing literature have examined the long-term effects of LAI antipsychotics on QoL and functioning (Ascher-Svanum et al., 2014; Giraud-Baro et al., 2016). In a study evaluating long-term olanzapine LAI treatment in patients with schizophrenia, mean QLS total score improved 6.8 points (64.0 to 70.8, $P < 0.001$) over the 2-year study period (Ascher-Svanum et al., 2014). Another study assessed global functioning using the Global Assessment of Functioning (GAF) rating scale in patients with schizophrenia after 1 year of treatment with risperidone LAI. An improvement of 5.8 ± 0.45 points was observed in the GAF scores. Social functioning also significantly improved in these patients (Giraud-Baro et al., 2016). Together with these studies, present findings emphasize the benefits of maintenance treatment with antipsychotics on functional improvement in patients with schizophrenia.

Mean CGI-S score upon entry to the extension study was reflective of mild disease severity. Patients maintained or showed incremental improvements in symptoms based on their CGI-S scores at the end of the extension study. There were no notable differences in baseline CGI-S scores or TEAEs between patients who started the study and those who completed the study, and the effectiveness of AOM 400 was maintained even when the discontinuations were considered by MMRM analysis. In a previous open-label, long-term maintenance study with AOM 400, CGI-S and Positive and Negative Syndrome Scale scores were also stable across the 52-week study, with a mean improvement of 0.14 points in CGI-S at last visit (Peters-Strickland et al., 2015). Together, these data support the continued clinical effectiveness of AOM 400 during long-term treatment.

Notably, 88 of the 100 eligible patients chose to enroll in the extension study, supporting the overall effectiveness and tolerability of AOM 400. Considering the substantial side effects associated with antipsychotic drugs and their potential detrimental impact on patient outcomes, the side effect profile is an important factor when choosing an antipsychotic for long-term maintenance treatment (Falkai et al., 2006; Hasan et al., 2013). In an open-label study in patients previously stabilized on oral olanzapine, 17.8% of patients had a $\geq 7\%$ increase in

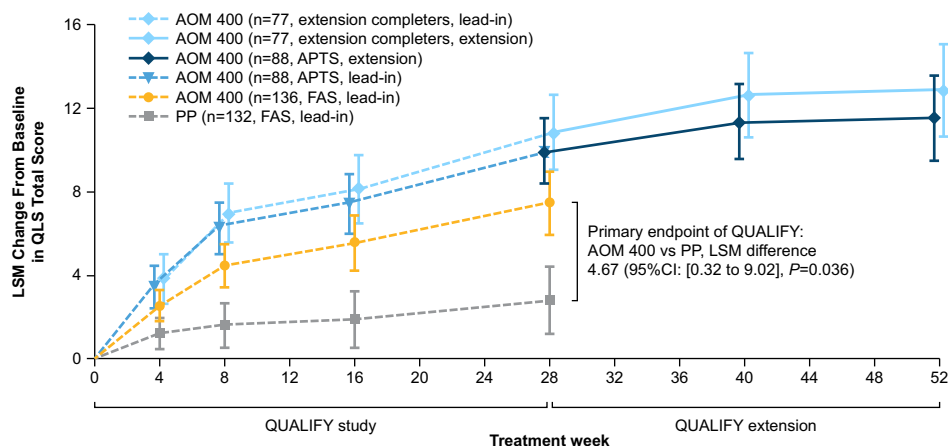


Fig. 2. Change in QLS total score from baseline to week 28 after AOM 400 or PP treatment in the QUALIFY study and to week 52 in patients continuing AOM 400 treatment in the extension study. LSM change from baseline was analyzed using the mixed model for repeated measures in the FAS of patients in the QUALIFY study and in the APTS in the extension study. Error bars indicate standard error. Week 0 corresponds to the randomization visit in the QUALIFY lead-in study; in QUALIFY, the first AOM 400 injection was given at week 4, patients were on oral aripiprazole in the interim. AOM 400 = aripiprazole once-monthly 400 mg; APTS = all-patients-treated set; FAS = full analysis set; LSM = least squares mean; PP = paliperidone palmitate; QLS = Heinrichs-Carpenter Quality of Life Scale.

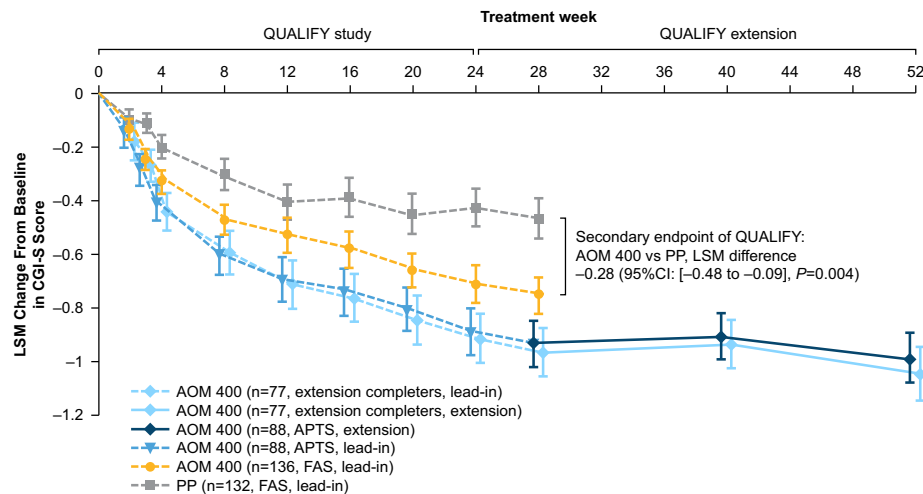


Fig. 3. Change in CGI-S score from baseline to week 28 after AOM 400 or PP treatment in the QUALIFY study and to week 52 in patients continuing AOM 400 treatment in the extension study. LSM change from baseline was analyzed using the mixed model for repeated measures in the FAS of patients in the QUALIFY study and in the APTS in the extension study. Error bars indicate standard error. Week 0 corresponds to the baseline visit in the QUALIFY lead-in study; in QUALIFY, the first AOM 400 injection was given at week 4, patients were on oral aripiprazole in the interim. AOM 400 = aripiprazole once-monthly 400 mg; APTS = all-patients-treated set; CGI-S = Clinical Global Impressions-Severity; FAS = full analysis set; LSM = least squares mean; PP = paliperidone palmitate.

weight from baseline with 6 months of treatment with olanzapine LAI (Mitchell et al., 2013). In another open-label study, patients switching from an LAI typical antipsychotic to risperidone LAI showed greater increases in body mass and prolactin compared with those who continued LAI typical antipsychotics at 12 months (Covell et al., 2012). In the present study, the incidence of weight gain was lower with AOM 400 compared with the lead-in study. Potentially clinically significant weight increase ($\geq 7\%$) was observed in 7% of patients in the extension study and 11% in the lead-in QUALIFY study. None of the patients demonstrated prolactin-related symptoms, and the incidence of EPS-related symptoms was also low. Overall, the safety findings from this study are consistent with the known safety profile of AOM 400 (Fleischacker et al., 2014; Kane et al., 2012; Naber et al., 2015; Peters-Strickland et al., 2015). No new safety concerns arose in the extension study. Although about half of the patients in the QUALIFY extension study experienced TEAEs, most TEAEs were mild or moderate in severity. The proportion of patients having AEs in the lead-in study was similar to that of the extension study, indicating that continued treatment with AOM 400 does not result in an increase in AEs over time. A low discontinuation rate further supports the long-term tolerability of AOM 400.

This study is associated with some limitations. It was an open-label extension study with no placebo or other comparator. Raters of QLS or CGI-S were not blinded to treatment assignment during the extension study. Additionally, the extension study participants had successfully completed the QUALIFY study in the AOM 400 group, thus comprising a population enriched with patients who tolerate AOM 400 treatment. Furthermore, the patients who experienced the most frequent or most bothersome AEs may not have completed the lead-in study or may have chosen not to participate in the extension. As with any extension study, the patients who enrolled were likely those who achieved good treatment response during the QUALIFY study and who were satisfied with their treatment, thus contributing to the maintained improvement. Indeed, MMRM analysis showed that the patients who entered and/or completed the extension study had numerically greater improvements in QLS and CGI-S by the end of QUALIFY than the QUALIFY full analysis set. Thus, a favorable selection bias could have contributed to the observed high study completion rate. Longer-term studies >1 year are needed to further establish the clinical benefit of maintenance treatment with AOM 400 in schizophrenia.

For chronic diseases, potential challenges with long-term treatment are reduced effectiveness over time (Emsley et al., 2013; Leucht et al., 2012) and long-term or worsening side effects. The adequate duration

of long-term maintenance treatment for schizophrenia is a matter of debate, although patients who discontinue treatment have been shown to have higher rates of relapses (Hasan et al., 2013; Kane et al., 2013). Therefore, although not definitively supported by evidence from randomized controlled trials, treatment guidelines recommend continued treatment with antipsychotics in stabilized patients. Results from the present study demonstrate that continued treatment with AOM 400 is a safe and effective option to maintain improvements in QoL and functioning.

5. Conclusions

In this 28-week open-label extension of the QUALIFY study, improvements in health-related QoL and functioning, as measured with QLS and CGI-S scales, were maintained with AOM 400 treatment. These results indicate that continued functional improvement could be a feasible goal in long-term treatment of schizophrenia. AOM 400 was well tolerated, with a low frequency of AEs consistent with the known safety profile of aripiprazole. These results further support the clinical benefits of AOM 400 for the long-term maintenance treatment of patients with schizophrenia.

Disclosures

Dieter Naber has participated in advisory boards for Janssen/Cilag, Eli Lilly, Lundbeck, Otsuka, and Servier; and has received speaker honoraria from Astra Zeneca, Janssen/Cilag, Eli Lilly, Lundbeck, and Otsuka; neither he nor his wife has stock in or other financial relationship to any company. Ross A. Baker and Timothy Peters-Strickland are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. Anna Eramo and Carlos Forray are employees of Lundbeck LLC. Christophe Sapin and Karina Hansen are employees of Lundbeck SAS. Anna-Greta Nylander, Peter Hertel, and Simon Nitschky Schmidt are employees of H. Lundbeck A/S. Jean-Yves Loze is an employee of Otsuka Pharmaceutical Europe. Steven G. Potkin has been a consultant or participated in advisory boards for Otsuka, Sunovion, Roche, Lundbeck, FORUM, Allergan, and Alkermes; has received grants or research support from Eli Lilly, Toyama, Otsuka, FORUM, Alkermes, Eisai, and Lundbeck; and has been a member of the speakers bureau or received speaker honoraria for Otsuka, Sunovion, Novartis, and Allergan.

Contributors

Dieter Naber was the signatory investigator on the study. Dieter Naber, Carlos Forray, Christophe Sapin, and Steven G Potkin contributed to the design of the study. All authors helped to interpret the data, reviewed each draft of the manuscript, and approved the final draft for submission.

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