Schizophrenia Research 168 (2015) 498–504

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia

Dieter Naber [a], Karina Hansen [b], Carlos Forray [c], Ross A. Baker [d], Christophe Sapin [b], Maud Beillat [b], Timothy Peters-Strickland [d], Anna-Greta Nylander [e], Peter Hertel [e], Henrik Steen Andersen [e], Anna Eramo [f], Jean-Yves Loze [g], Steven G. Potkin [h,*]

[a] Department for Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany
[b] Lundbeck SAS, Quai du Président Roosevelt 37-45, 92445 Issy-les-Moulineaux, France
[c] Lundbeck Research US, 215 College Rd, Paramus, NJ 07652, United States
[d] Otsuka Pharmaceutical Development & Commercialization, Inc., 508 Carnegie Center, Princeton, NJ 08540, United States
[e] H. Lundbeck A/S, Ottiliavej 9, 2500 Valby, Denmark
[f] Lundbeck LLC, 4 Parkway North, Deerfield, IL 60015, United States
[g] Otsuka Pharmaceutical Europe Ltd, Gallions Wexham Springs, Framewood Road, Wexham SL3 6PJ, United Kingdom
[h] Department of Psychiatry and Human Behavior, University of California, Irvine, 5251 California Ave, Irvine, CA 92617, United States

ARTICLE INFO

Article history:
Received 12 May 2015
Received in revised form 1 July 2015
Accepted 6 July 2015
Available online 29 July 2015

Keywords:
Antipsychotic treatment
Clinical trial
Long-acting injectable
Aripiprazole
QLS
Functioning

ABSTRACT

Objective: To directly compare aripiprazole once-monthly 400 mg (AOM 400) and paliperidone palmitate once-monthly (PP) on the Heinrichs–Carpenter Quality-of-Life Scale (QLS), a validated health-related quality of life and functioning measure in schizophrenia.
Method: This 28-week, randomized, non-inferiority, open-label, rater-blinded, head-to-head study (QUALIFY) of AOM 400 and PP in adult patients (18–60 years) comprised oral conversion, initiation of AOM 400 or PP treatment, and continuation with intramuscular injections every 4 weeks. The primary endpoint assessed non-inferiority and superiority on QLS total score analyzed using a mixed model for repeated measurements.
Results: Of 295 randomized patients, 100/148 (67.6%) of AOM 400 and 83/147 (56.5%) of PP patients completed 28 weeks of treatment. A statistically significant least squares mean difference in change from baseline to week 28 on QLS total score (4.67 [95%CI: 0.32;9.02], p = 0.036) confirmed non-inferiority and established superiority of AOM 400 vs PP. There were also significant improvements in Clinical Global Impression — Severity scale and the Investigator's Assessment Questionnaire for AOM 400 vs PP, and pre-defined sub-group analyses revealed a consistent pattern of significance favoring AOM 400 in patients ≤35 years. Common treatment-emergent adverse events in the treatment continuation phase were more frequent with PP vs AOM 400, and adverse events were the most frequent reason for discontinuation (27/137 [19.7%] for PP and 16/144 [11.1%] for AOM 400). All-cause discontinuation was numerically lower with AOM 400.
Conclusion: Superior improvements on clinician-rated health-related quality of life and a favorable tolerability profile suggest greater overall effectiveness for aripiprazole once-monthly vs paliperidone palmitate.
ClinicalTrials.gov identifier: NCT01795547.

1. Introduction

Schizophrenia is a chronic disorder characterized by frequent relapses that have severe consequences for patients' quality of life, including occupational and psychosocial function, as well as economic burden for the patients and their families. Since patients may not return to previous levels of functioning following relapse (Emsley et al., 2013; Lieberman et al., 2006), early treatment intervention is important and has the potential to change the course of the illness (Stahl, 2014). Another prerequisite for successful treatment is patient adherence, which is often poor in schizophrenia (Perkins, 2002).

Long-acting injectable antipsychotics (LAIs) may increase long-term adherence to treatment and may reduce the risk of relapse and improve patient functioning (Kishimoto et al., 2013). Both aripiprazole once-monthly 400 mg (AOM 400) and paliperidone palmitate once-monthly (PP) are atypical LAIs with demonstrated efficacy in schizophrenia (Fleischhacker et al., 2014; Hough et al., 2010; Kane et al., 2012; Nasrallah et al., 2010). However, they have different pharmacological mechanisms: aripiprazole is a partial agonist at dopamine D_2 and serotonin 5-HT_{1A} receptors and an antagonist at $5HT_{2A}$ receptors while paliperidone is an antagonist at D_2 and $5HT_{2A}$ receptors. In addition to

* Corresponding author.

http://dx.doi.org/10.1016/j.schres.2015.07.007

efficacy, an acceptable tolerability profile is important for long-term treatment (Hasan et al., 2013), and studies of treatment effectiveness (comprising both efficacy and tolerability) on more clinically relevant endpoints beyond traditional psychopathology are necessary to evaluate the effect of treatments on patient functioning and quality of life, both of which are inversely predictive of relapse (Boyer et al., 2013).

The Heinrichs–Carpenter Quality-of-Life Scale (QLS) was selected as the primary endpoint reflecting a key long-term treatment goal for both clinician and patient. It is a clinician-rated scale derived from a semi-structured patient interview that is widely used in psychopharmacological evaluation of treatments for schizophrenia (Lewis et al., 2006). The QLS is a health-related quality-of-life scale focused on intrapsychic, social, and negative symptoms and their consequences for functioning in schizophrenia (Heinrichs et al., 1984). The QLS total score measures effects beyond functioning in patients with schizophrenia; it also assesses the richness of personal experience, the quality of interpersonal relations, and productivity in occupational roles.

The QUALIFY (*QUA*lity of *LI*fe with Abili*FY* Maintena®) study is one of very few randomized studies that directly compare two atypical LAIs and is the first to compare two atypical LAIs with different mechanisms of action on health-related quality of life and functioning. Previous head-to-head studies have compared effects of LAIs on classical measures of psychopathology and have consistently showed non-inferiority between different LAIs (Fleischhacker et al., 2012; Li et al., 2011; Pandina et al., 2011). Superiority of one atypical LAI vs another has not been previously demonstrated.

The primary objective of this study was to compare the effectiveness of 28-week treatment with AOM 400 to PP in adult patients with schizophrenia on the QLS using a non-inferiority hypothesis; if met, a predefined test of superiority would be conducted. Additional objectives were to compare safety and tolerability of the treatments.

2. Materials and methods

2.1. Study design

This phase 3b, multicenter, 28-week, open-label, rater-blinded, randomized, non-inferiority study (NCT01795547) compared the effectiveness of two atypical LAIs, AOM 400 (reduction of the maintenance dose to 300 mg based on individual patient tolerability was permitted) and PP (flexible dosing, per label, with 50 to 150 mg/month as paliperidone [EU and Canada], equivalent to 78 to 234 mg/month as paliperidone palmitate [US]). The study design is illustrated in Fig. 1.

Patients were enrolled from 71 study sites in 10 countries (Canada, Czech Republic, Germany, Estonia, Spain, France, United Kingdom, Italy, Sweden, United States). The study took place from February 2013 through September 2014 and was in compliance with the principles of Good Clinical Practice and in accordance with the Declaration of Helsinki.

2.2. Patients

Eligible patients included men and women aged 18 to 60 years, with DSM-IV-TR–defined schizophrenia. The study included stable, i.e., not acutely psychotic, patients needing a change from current oral antipsychotic treatment due to inadequate response, poor tolerability, or lack of adherence and who, in the judgment of the investigator, would benefit from LAI treatment. A Clinical Global Impression — Severity scale (CGI-S) score ≥3 (mildly ill) and ≤5 (markedly ill) was required at both the screening and baseline visits, and treatment with oral antipsychotics was required for 3 months prior to screening. To allow prespecified comparisons of changes in outcome measures for younger and older cohorts, randomization was stratified by age, and recruitment targeted one third of patients ≤35 years.

Patients with a diagnosis of psychiatric disorder or Axis I disorder (DSM-IV-TR criteria) other than schizophrenia, substance use disorder (except nicotine) that according to the investigator's judgment could compromise the patient's compliance with the study procedures, intolerance to or previous lack of efficacy with oral aripiprazole, risperidone, or paliperidone, or previous treatment with LAIs within 6 months prior to screening were excluded from participation in the study. Based on disease severity criteria, patients exhibiting acute exacerbation of psychotic symptoms, hospitalization for >3 months at the time of the screening visit, at significant risk of harming self or others, refractoriness to antipsychotic treatment, or with a history of failure to respond to/responding only to clozapine treatment were also excluded.

2.3. Assessments

The primary endpoint was change from baseline to week 28 on the QLS total score. The QLS consists of 21 items in 4 domains: Interpersonal Relations (8 items), Instrumental Role (4 items), Intrapsychic

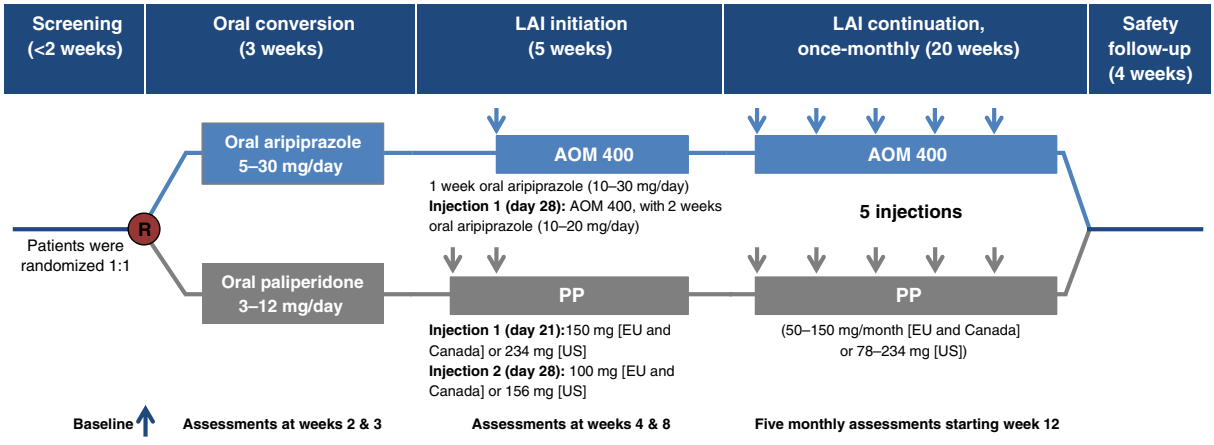

Fig. 1. Study design. After screening for 7–14 days, eligible patients were randomly assigned (1:1) to AOM 400 or PP treatment groups. The study comprised three phases: (i) a 3-week conversion period to either oral aripiprazole (5–30 mg/day) or oral paliperidone (3–12 mg/day) during which patients were tapered from previous antipsychotic medication(s) while gradually increasing doses of oral aripiprazole or paliperidone. (ii) Patients who tolerated oral medication initiated the assigned LAI treatment with AOM 400 or PP in a 5-week phase. Patients randomized to AOM 400 continued with one week of oral aripiprazole treatment, then received the first intramuscular (IM) injection at week 4, accompanied by 2 weeks of concurrent oral aripiprazole treatment (recommended supplemental dose was 10–20 mg/day depending on previous dose). Patients randomized to PP received one IM injection (150 mg [EU and Canada], 234 mg [US]) at the end of week 3 and discontinued oral paliperidone. One week later, a second PP IM injection was given (100 mg [EU and Canada], 156 mg [US]). (iii) LAI treatment continued as five monthly injections of AOM 400 or PP, starting at week 8. Injections could be given up to two days before or five days after the scheduled monthly dose. Patients who received at least one dose of study medication were followed for safety for 4 weeks after the last study visit.

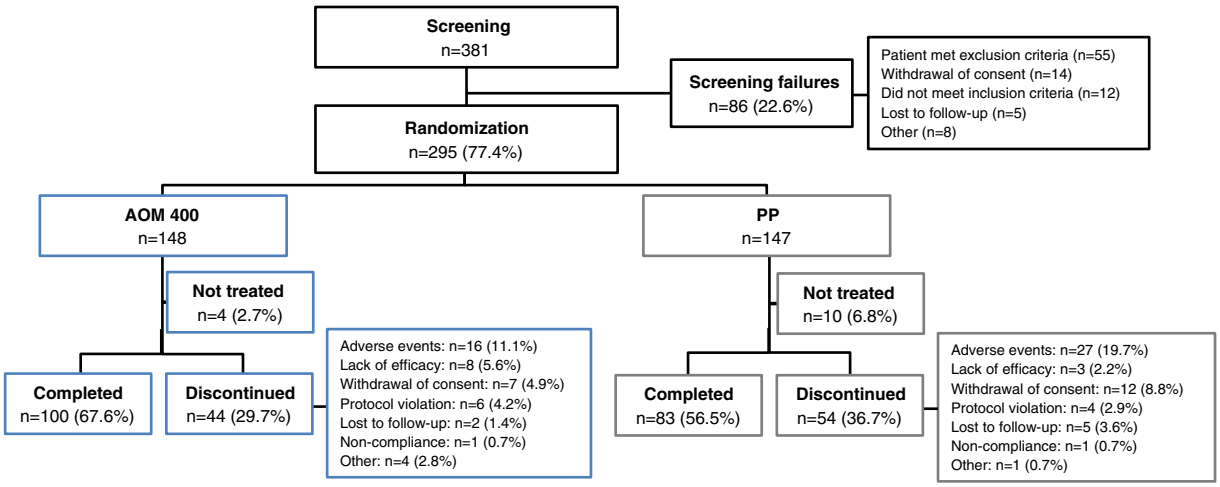

Fig. 2. Patient disposition and primary reason for discontinuation and screening failure. Discontinuation percentages are calculated based on the number of treated patients. Each patient could have more than one reason for screening failure. One patient in the PP group did not complete the study completion panel in a late visit, therefore no reason for discontinuation was recorded.

Foundations (7 items), and Common Objects and Activities (2 items). Each item was scored on a 7-point Likert scale, from 0 (severe impairment) to 6 (normal or unimpaired functioning). The score is calculated for each domain and the total score ranges from 0 to 126.

The CGI-S provides the clinician's impression of the patient's current state of mental illness on a 7-point scale ranging from 1 (normal–not at all ill) to 7 (among the most extremely ill patients) (Guy, 1976). The Investigator's Assessment Questionnaire (IAQ) is a validated, clinician-rated scale designed to assess relative effectiveness (efficacy, safety and tolerability) of antipsychotic medications in patients with schizophrenia (Tandon et al., 2005). The IAQ consists of 12 equally weighted items: positive symptoms, negative symptoms, other efficacy symptoms, somnolence, weight gain, signs and symptoms of prolactin elevation, akathisia, other extrapyramidal symptoms, other safety or tolerability issues, cognition, energy, and mood. For each item, the current medication is compared with previous antipsychotic medication on a five-point scale from 1 (much better) to 5 (much worse). Total IAQ scores range from 12 to 60 with lower IAQ total scores indicating better relative treatment effectiveness.

The QLS and IAQ scales were administered by a rater blinded to the treatment (without access to medical records, study files, or study medications) trained for consistency and reliability. Raters for the remaining assessments and questionnaires were not blinded to the patient's treatment. IAQ and CGI-S were pre-defined secondary endpoints. Additional endpoints will be reported elsewhere.

2.4. Statistical analyses

A difference of 5 points on QLS total score was defined as clinically meaningful in a comparative effectiveness study (CUtLASS) between first- and second-generation antipsychotics (Jones et al., 2006). This was supported by results from the STAR study (Taylor et al., 2008) in which a difference of 6 points between aripiprazole and standard of care was observed. Therefore, the study was powered based on a 5-point non-inferiority margin (Wiens, 2002). Assuming an SD of 15 in the change from baseline to week 28, a treatment difference of 1, a power of 80%, and a 30% discontinuation rate, the total sample size was set to 286.

All effectiveness analyses were conducted using the full analysis set (FAS), which was defined as treated patients who had a valid QLS baseline and ≥1 post-baseline QLS assessment. The safety sample included all patients who received at least one dose of study medication (oral or LAI). All effectiveness endpoints were analyzed using a mixed model for repeated measures (MMRM) with an unstructured covariance matrix including baseline score-by-visit interaction, geographic region (Europe/North America), age subgroup (≤35/>35 years), visit, and treatment-by-visit interaction as fixed effects. Estimated treatment differences (AOM 400 vs PP) and associated tests were made at all study visits.

For the pre-defined primary endpoint, non-inferiority criterion was met if the lower bound of the two-sided 95% CI was greater than −5 (non-inferiority margin) for the mean treatment difference in change from baseline in QLS at week 28 (AOM 400 vs PP). The pre-defined statistical analysis plan allowed for subsequent testing for superiority of AOM 400 over PP which was considered confirmed if the lower bound of the two-sided 95% CI was >0. As pre-defined sensitivity analysis on the primary endpoint, change from baseline to week 28 of QLS total

Table 1
Patient baseline demographics and disease severity.

	Aripiprazole once-monthly 400 mg (AOM 400)	Paliperidone palmitate once-monthly (PP)
Patients randomized, n	148	147
Patients treated, n (%)	144 (97.3)	137 (93.2)
Age, mean (SD), years	42.6 (10.9)	41.2 (10.7)
Age, n (%):		
≤35 years	42 (29.2)	38 (27.7)
>35 years	102 (70.8)	99 (72.3)
Age at schizophrenia onset, mean (SD), years	28.5 (10.7)	26.8 (9.5)
Gender male, n (%)	86 (59.7)	82 (59.9)
Race, n (%):		
White	101 (70.1)	95 (69.3)
Black or African American	41 (28.5)	35 (25.5)
Asian	1 (0.7)	3 (2.2)
Other	0 (0.0)	3 (2.2)
Unknown	1 (0.7)	1 (0.7)
BMI, mean (SD)	29.9 (6.3)[a]	29.1 (6.3)
<18.5 kg/m^2, n (%)	0 (0.0)	1 (0.7)
18.5 to <25 kg/m^2, n (%)	30 (20.8)	35 (25.5)
25 to <30 kg/m^2, n (%)	50 (34.7)	50 (36.5)
≥30 kg/m^2, n (%)	63 (43.8)	51 (37.2)
Baseline severity scores:		
Full analysis set (FAS), n (%)	136	132
QLS total score, mean (SD)	66.0 (21.7)	62.9 (21.5)
CGI-S score, mean (SD)	4.0 (0.65)	4.0 (0.65)

There were no significant differences in demographics or baseline disease severity between patients in the AOM 400 and PP groups. BMI: body mass index, CGI-S: Clinical Global Impression — Severity of Illness, SD: Standard deviation, QLS: Heinrichs–Carpenter Quality-of-Life Scale.

[a] n = 143.

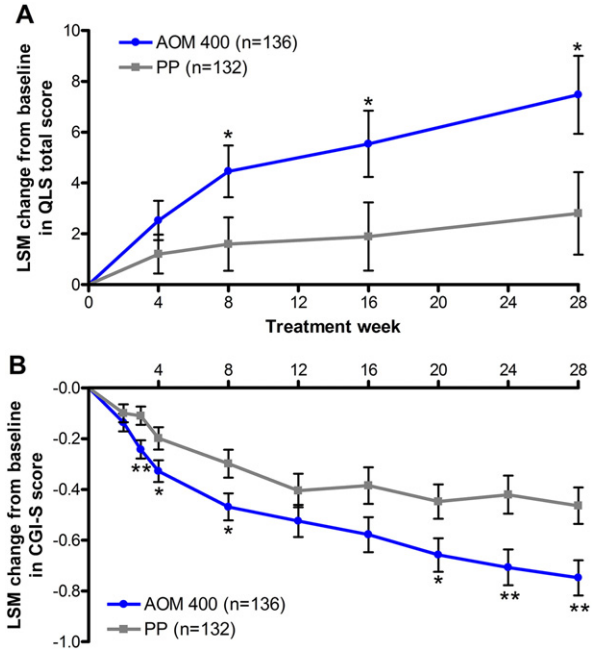

Fig. 3. Effects of AOM 400 and PP treatment on QLS total scores (A) and CGI-S scores (B). Least squares mean (LSM) changes from baseline were analyzed using a mixed model for repeated measures (MMRM). *p < 0.05, **p < 0.01 indicate significant differences between treatments (AOM 400 vs PP). Error bars indicate the standard error of the LSM.

score was assessed in the per-protocol set (PPS) with similar MMRM model as in the primary analysis. The PPS comprised all patients in the FAS who did not use disallowed concomitant medication during the treatment period, had at least one IM injection of AOM 400 or PP, and were rated on QLS and IAQ by a blinded rater (n=122 for AOM 400, n=112 for PP). Additional pre-defined sensitivity analyses included analysis of co-variance (ANCOVA) using last-observation-carried-forward (LOCF) and observed cases (OC) in the FAS.

In pre-defined analyses to investigate the effect of age on treatment outcome, all effectiveness endpoints were analyzed separately in patients ≤35 years and in those >35 years. Due to the reduced statistical power, these sub-group analyses were considered exploratory. For the continuous secondary endpoints (CGI-S and IAQ total score, and QLS domain scores), a similar methodology as described for the primary superiority analysis was applied. For all secondary analyses, differences between treatments were tested for significance; however, p-values were considered nominal and were not corrected for multiple comparisons.

The proportions of patients with an adverse event (AE) are shown using descriptive statistics. A treatment-emergent AE (TEAE) was defined as an AE that started at or after the date of first dose of oral treatment and prior to the last protocol-specified contact with each patient. TEAEs were allocated to treatment phases according to the time of onset as follows. Oral conversion: a TEAE with onset on or after the date of first oral dose and prior to the LAI treatment initiation period (after week 3). LAI treatment initiation: a TEAE with onset at or after week 3 and prior to week 8. LAI treatment continuation: a TEAE with onset at or after week 8 and prior to the completion visit (week 28). TEAEs that increased in severity across periods were counted in both periods.

3. Results

3.1. Patient disposition and exposure

The study randomized 295 patients of whom 67.6% (100/148) in the AOM 400 and 56.5% (83/147) in the PP group completed 28 weeks of treatment (Fig. 2). At baseline, the treated patients (n=281) were stable and showed similar characteristics as well as similar levels of functional impairment and psychopathology between treatment groups (Table 1). The mean dose of AOM 400 at week 24 was 387 ± 3.4 mg (±SE). The mean PP dose at week 24 of the study was 110 ± 3.6 mg (±SE, EU dosing) equivalent to 172 mg (US dosing).

3.2. Effectiveness outcomes

Analysis of the pre-defined primary endpoint showed a least squares mean (LSM) change from baseline to week 28 on QLS total score of 7.47 ± 1.53 for AOM 400 (n=136) and 2.80 ± 1.62 for PP (n=132). The LSM difference between treatments was 4.67 (95%CI: [0.32;9.02], p=0.036) confirming non-inferiority of AOM 400 compared to PP as the lower bound of the 95%CI was > −5. Sensitivity analyses of the primary endpoint all demonstrated non-inferiority of AOM 400 vs PP using MMRM with the PPS, LOCF ANCOVA with the FAS and OC ANCOVA with the FAS. Superiority was then tested as pre-specified with the FAS and demonstrated for AOM 400 over PP, since the lower bound of the 95%CI was >0. Improvements on QLS total scores for AOM 400 vs PP were significant at 8 weeks of treatment and at all subsequent visits (Fig. 3A).

AOM 400 treatment also resulted in significant improvements relative to PP in CGI-S (Fig. 3B) and IAQ scores (Table 2). The LSM difference between treatments in change from baseline to week 28 on CGI-S score was −0.28 (95%CI: [−0.48; −0.09], p=0.004).

Pre-defined secondary analyses of change from baseline to week 28 in QLS domain scores showed that the intrapsychic foundations domain of the QLS significantly improved after AOM 400 treatment as compared to PP treatment, whereas the treatment differences, although in favor of AOM 400, did not reach significance in the other QLS domains (Table 3).

Additional pre-defined analyses of secondary outcomes found significant LSM treatment differences at week 28 favoring AOM 400 vs PP in patients ≤35 years on QLS (10.7, 95%CI: [0.70;20.7], p=0.037), CGI-S (−0.44, 95%CI: [−0.83; −0.06], p=0.026), and IAQ (−2.65, 95%CI: [−5.28; −0.02], p=0.048) (Fig. 4, Table 2). Similar analyses in patients >35 years showed no significant LSM treatment differences on QLS (2.81, 95%CI: [−2.02;7.63], p=0.25), CGI-S (−0.22, 95%CI: [−0.44;0.01], p=0.061), or IAQ (−1.02, 95%CI: [−2.77;0.73], p=0.25).

Table 2
Effects of AOM 400 and PP treatment on IAQ total scores at week 28 in the total and in age-stratified subgroups.

	LSM IAQ total score at week 28 (SE)		LSM difference, AOM 400 vs PP (95% CI)[a]	p-Value
FAS	AOM 400 (n=133)	PP (n=131)		
	32.32 (0.52)	33.81 (0.55)	−1.49 (−2.94, −0.05)	0.043
Patients ≤35 years, FAS	AOM 400 (n=40)	PP (n=37)		
	31.59 (0.86)	34.24 (1.02)	−2.65 (−5.28, −0.02)	0.048
Patients >35 years, FAS	AOM 400 (n=93)	PP (n=94)		
	32.52 (0.62)	33.55 (0.63)	−1.02 (−2.77, 0.73)	0.250

FAS: full analysis set, LSM: least squares mean, SE: standard error.
[a] Pre-defined secondary analysis used MMRM to assess treatment effect on IAQ total scores at week 28. IAQ measures treatment effectiveness relative to previous medication. Patients with non-missing data in the FAS are analyzed.

Table 3
Effects of AOM 400 and PP treatment on QLS domain scores from baseline to week 28.

	LSM change from baseline to week 28 (SE)		LSM difference, AOM 400 vs PP (95% CI)[a]	p-Value
	AOM 400 (n=136)	PP (n=132)		
Common objects and activities	0.52 (0.16)	0.18 (0.17)	0.33 (−0.12, 0.78)	0.149
Intrapsychic foundations	2.25 (0.59)	0.50 (0.63)	1.75 (0.09, 3.41)	0.039
Interpersonal relations	3.24 (0.68)	1.47 (0.72)	1.76 (−0.14, 3.67)	0.070
Instrumental role	1.76 (0.42)	0.83 (0.45)	0.92 (−0.28, 2.12)	0.130

LSM: least squares mean, SE: standard error.
[a] Pre-defined secondary analysis used similar MMRM analyses as for the primary endpoint to assess changes from baseline on individual QLS domains to week 28 in the full analysis set.

3.3. Safety and tolerability

AEs were the most frequent reason for discontinuation; AOM 400: 11.1% (16/144), PP: 19.7% (27/137). All-cause discontinuations, discontinuations due to AEs and withdrawal of consent were numerically lower for AOM 400 as compared to PP (Fig. 2).

TEAEs occurring in ≥5% of patients in either treatment group are shown in Table 4. The most frequent TEAEs in the treatment continuation phase (the main period of interest with respect to safety evaluation of AOM 400 vs PP) were increased weight, psychotic disorder, and insomnia, which were all more frequent in PP-treated patients. TEAEs related to extrapyramidal symptoms, including akathisia, were low and occurred at rates less than 5% in both groups. In treated patients, the absolute mean change (±SD) in body weight from baseline to week 28 was 0.2 ± 5.9 kg (n=100) for AOM 400 and 1.4 ± 6.6 kg for PP (n=83). Furthermore, the incidences of potential clinically significant weight gain (≥7% change from baseline) at any time post-baseline were 16/144 (11.1%) for AOM 400 and 20/137 (14.6%) for PP, while corresponding incidences of weight loss were 14/144 (9.7%) for AOM 400 and 8/137 (5.8%) for PP. No new safety signals were detected in either treatment group, and the incidence of serious AEs was low with both treatments. No deaths occurred during the study.

4. Discussion

The pre-defined primary endpoint showing superior improvements with AOM 400 vs PP on health-related quality of life measured with QLS was supported by secondary outcome measures (CGI-S and IAQ) showing greater improvements in clinical symptoms and treatment effectiveness with AOM 400 vs PP.

Although this study was randomized, it was designed to be more naturalistic than traditional pivotal studies with regards to inclusion criteria. The low frequency of screening failures (22.6%) suggests that the study did not recruit a highly selected patient group, which is consistent with a naturalistic setting. A health-related quality-of-life measure was selected as the primary endpoint in order to capture benefits beyond traditional measures of symptomatic efficacy. Therefore, these study results may be expected to be relevant to patient populations in a real-world setting.

This study is the first to use a health-related quality-of-life scale as primary endpoint to compare two LAIs in the treatment of schizophrenia and is also the first to show superiority of one atypical LAI over another. The numerical LSM changes from baseline to week 28 in the AOM 400 group observed in the primary analysis of QLS total score (7.47 points) may, in contrast to PP (2.80 points), be considered clinically relevant (Jones et al., 2006; Thwin et al., 2013). The difference in QLS total scores between AOM 400 and PP in LSM change from baseline to week 28 (4.67 points) is close to the minimal clinically important difference of 5.3 points previously defined (Falissard et al., in press). The QLS domain analysis suggests that improvements in the underlying intrapsychic foundations, such as sense of purpose, curiosity, empathy, and emotional interaction, contribute most to the greater improvement in functioning observed on QLS total scores with AOM 400 vs PP treatment in patients with schizophrenia. Typical efficacy assessments do not focus on the more subtle aspects of social functioning that define the richness of personal experience. We speculate that the improvements on health-related quality of life and functioning with AOM 400 vs PP may be attributed to the characteristics and profile of the therapeutically active molecule. In contrast to paliperidone, which completely blocks dopamine D_2 receptors, aripiprazole is a partial agonist at dopamine D_2 receptors, which are hypothesized to modulate dopaminergic activity in the brain, thereby reducing positive symptoms and potentially improving negative and cognitive symptoms (Lieberman, 2004).

AOM 400 showed greater effectiveness than PP on primary and secondary endpoints in the total study population. In pre-defined analyses, similar significant effects with AOM 400 vs PP were consistently found in patients ≤35 years. Numerically larger improvements from baseline were also observed after AOM 400 treatment compared with PP in patients >35 years, but no significant differences were shown. Based on the positive effect of AOM 400 in younger patients, an early treatment start may help to protect patients from subsequent deterioration in

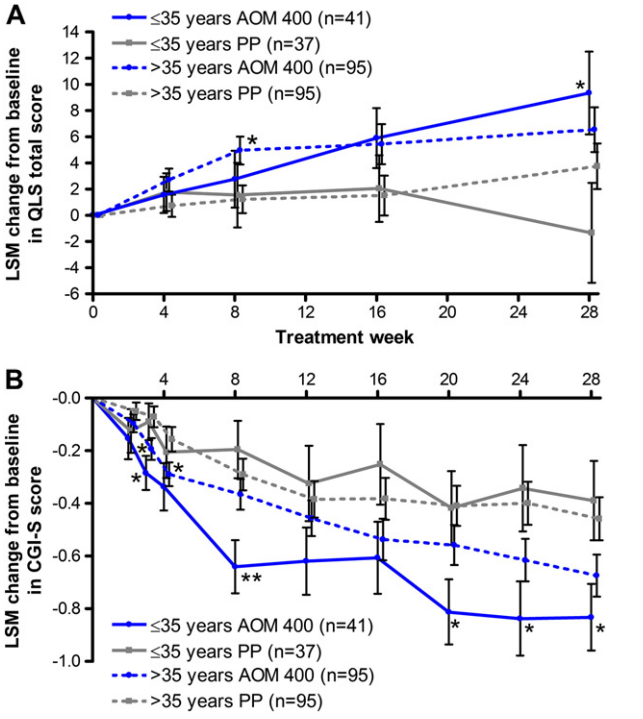

Fig. 4. Effects of AOM 400 and PP treatment on QLS total score (A) and CGI-S score (B) in patients ≤35 years and in those >35 years. This pre-defined analysis assessed least squares mean (LSM) changes from baseline in age-stratified subgroups using same method as for the primary endpoint (MMRM, FAS). *p < 0.05, **p < 0.01 indicate significant differences between treatments (AOM 400 vs PP) within each age-group. Error bars indicate the standard error of the LSM. In treated patients ≤35 years, baseline QLS scores were 67.5 ± 21.6 for AOM 400 and 64.1 ± 24.6 for PP, baseline CGI-S scores were 3.95 ± 0.62 for AOM 400 and 4.00 ± 0.57 for PP; in treated patients >35 years, baseline QLS scores were 65.7 ± 21.3 for AOM 400 and 61.9 ± 20.1 for PP, baseline CGI-S scores were 4.01 ± 0.67 for AOM 400 and 3.96 ± 0.68 for PP.

Table 4
Treatment-emergent adverse events (TEAEs) by treatment group and phase.[a]

Treatment phase:	Oral conversion		LAI initiation		LAI continuation	
Treatment group:	AOM 400 (n=144)	PP (n=137)	AOM 400 (n=132)	PP (n=118)	AOM 400 (n=119)	PP (n=109)
n (%):						
Any TEAE	50 (34.7)	53 (38.7)	55 (41.7)	51 (43.2)	62 (52.1)	72 (66.1)
Any SAE	2 (1.4)	1 (0.7)	2 (1.5)	1 (0.8)	6 (5.0)	8 (7.3)
TEAE leading to discontinuation	6 (4.2)	10 (7.3)	4 (3.0)	6 (5.1)	6 (5.0)	13 (11.9)
Specific TEAEs occurring in ≥5% of patients in any group, n (%):						
Accidental overdose[b]	11 (7.6)	11 (8.0)	19 (14.4)	2 (1.7)	2 (1.7)	1 (0.9)
Injection site pain	N/A	N/A	1 (0.8)	10 (8.5)	3 (2.5)	1 (0.9)
Insomnia	11 (7.6)	4 (2.9)	4 (3.0)	8 (6.8)	3 (2.5)	6 (5.5)
Nausea	2 (1.4)	8 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Psychotic disorder	2 (1.4)	0 (0.0)	2 (1.5)	0 (0.0)	3 (2.5)	6 (5.5)
Weight increased	0 (0.0)	2 (1.5)	1 (0.8)	1 (0.8)	12 (10.1)	17 (15.6)
TEAEs related to extrapyramidal symptoms, n (%):						
Akathisia	4 (2.8)	2 (1.5)	3 (2.3)	3 (2.5)	2 (1.7)	2 (1.8)
Dystonia	1 (0.7)	0 (0.0)	2 (1.5)	1 (0.8)	1 (0.8)	0 (0.0)
Extrapyramidal disorder	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle rigidity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Muscle spasms	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Tremor	0 (0.0)	0 (0.0)	1 (0.8)	2 (1.7)	2 (1.7)	2 (1.8)

AOM 400: aripiprazole once-monthly 400 mg, LAI: long-acting injectable, PP: paliperidone palmitate once-monthly, SAE: serious adverse event.
[a] Results shown from the safety sample (all treated patients).
[b] Some patients took more tablets than prescribed, in particular during the switch from oral medication to LAI treatment. These occurrences (monitored by pill counts at all visits) were reported as TEAEs 'accidental overdose' even though they were not SAEs and had no clinical relevance.

functioning (Emsley et al., 2013; Stahl, 2014; Tiihonen et al., 2011). These results speak in favor of initiating treatment with AOM 400 in younger patients as the greater treatment effectiveness may be particularly pronounced in this patient subgroup.

Both treatments were generally well tolerated, and the incidence of specific TEAEs was in line with the tolerability profile of AOM 400 and PP described in previous studies (Fleischhacker et al., 2013; Nasrallah et al., 2010). Due to the differences in the LAI initiation phase between AOM 400 and PP, the most valid comparison of tolerability between AOM 400 and PP is in the LAI continuation phase, where rates of common TEAEs were generally higher with PP as compared to AOM 400 treatment. Higher rates of TEAEs are consistent with the higher discontinuation rate due to AEs and numerically higher all-cause discontinuations with PP vs AOM 400. Overall, 44/148 (29.7%) receiving AOM 400 discontinued treatment compared to 54/147 (36.7%) receiving PP; discontinuations from the study for lack of efficacy were low in both treatment groups, and differences were neither statistically nor clinically significant.

As a randomized open-label study, certain limitations of the study are present. The patients' willingness to take LAI medication and knowledge of treatment assignment may have biased reporting. The treatment differences rated by the blinded clinician (QLS and IAQ) were similar to those rated by the non-blinded clinician (CGI-S). Although superior effectiveness of AOM 400 vs PP was found in the current study cohort, all patients should be evaluated on an individual basis for appropriate treatment choices.

5. Conclusions

In a head-to-head comparison, treatment with AOM 400 showed superior improvements to PP on health-related quality of life as measured with the clinician-rated QLS in schizophrenia. The observed changes in the QLS total score represent a clinically relevant improvement in functioning, including sense of purpose, motivation, empathy, and emotional interaction. The primary results were supported by significant treatment differences in CGI-S and IAQ scores, indicating an improvement in clinical symptoms and better effectiveness with AOM 400 compared to PP. In addition to improvements in symptoms and functioning, a favorable tolerability profile including lower incidences of relevant AEs and a numerically lower all-cause discontinuation rate suggest greater overall effectiveness for AOM 400 vs PP. In predefined analyses, significantly greater improvements with AOM 400 vs PP were consistently demonstrated in patients ≤35 years, indicating that younger patients may benefit in particular from AOM 400 compared to PP treatment.

Funding source
This study was funded by H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc.

Contributions
Naber D was the signatory investigator on the study. Naber D and Potkin SG contributed to the concept and design of the study. All authors contributed to the interpretation of the data, revised the manuscript, and approved the final content of the manuscript.

Conflict of interest
The findings of this study were presented at the 23rd European Congress of Psychiatry (EPA) held in Vienna, Austria on March 30, 2015, at the 15th International Congress on Schizophrenia Research held in Colorado Springs, Colorado, USA on March 29, 2015.

Dr. Naber has received speakers' honoraria from, or has served as a consultant to Lundbeck, Otsuka, AstraZeneca, Janssen/Cilag, Eli Lilly and Servier. Dr. Potkin has received research support or speakers' honoraria from, or has served as a consultant to Lundbeck, Otsuka, Sunovion, Roche, FORUM, Alkermes, Eli Lilly, Toyama, Eisai, Novartis, and Forest. Hansen, Sapin and Beillat are employees of Lundbeck SAS. Dr. Forray is an employee of Lundbeck Research. Nylander, Hertel, and Andersen are employees of H. Lundbeck A/S. Dr. Eramo is an employee of Lundbeck LLC. Baker and Dr. Peters-Strickland are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. Dr. Loze is an employee of Otsuka Pharmaceutical Europe Ltd.

Acknowledgments
The authors thank the patients participating in the study and their caretakers. We acknowledge Anders Ettrup, PhD (H. Lundbeck A/S) for medical writing assistance with the manuscript.

References

Boyer, L., Millier, A., Perthame, E., Aballea, S., Auquier, P., Toumi, M., 2013. Quality of life is predictive of relapse in schizophrenia. BMC Psychiatry 13, 15.
Emsley, R., Chiliza, B., Asmal, L., 2013. The evidence for illness progression after relapse in schizophrenia. Schizophr. Res. 148, 117–121.
Falissard, B., Sapin, C., Loze, J.Y., Landsberg, W., Hansen, K., 2015. Defining the minimal clinically important difference of the Heinrichs–Carpenter Quality of Life Scale (QLS). Int. J. Methods Psychiatr. Res. (in press).
Fleischhacker, W.W., Gopal, S., Lane, R., Gassmann-Mayer, C., Lim, P., Hough, D., Remmerie, B., Eerdekens, M., 2012. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. Int. J. Neuropsychopharmacol. 15, 107–118.
Fleischhacker, W.W., Sanchez, R., Johnson, B., Jin, N., Forbes, R.A., McQuade, R., Baker, R.A., Carson, W., Kane, J.M., 2013. Long-term safety and tolerability of aripiprazole once-

monthly in maintenance treatment of patients with schizophrenia. Int. Clin. Psychopharmacol. 28, 171–176.
Fleischhacker, W.W., Sanchez, R., Perry, P.P., Jin, N., Peters-Strickland, T., Johnson, B.R., Baker, R.A., Eramo, A., McQuade, R.D., Carson, W.H., Walling, D., Kane, J.M., 2014. Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study. Br. J. Psychiatry 205, 135–144.
Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. Government Printing Office, Washington, DC.
Hasan, A., Falkai, P., Wobrock, T., Lieberman, J., Glenthoj, B., Gattaz, W.F., Thibaut, F., Moller, H.J., 2013. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J. Biol. Psychiatry 14, 2–44.
Heinrichs, D.W., Hanlon, T.E., Carpenter Jr., W.T., 1984. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr. Bull. 10, 388–398.
Hough, D., Gopal, S., Vijapurkar, U., Lim, P., Morozova, M., Eerdekens, M., 2010. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr. Res. 116, 107–117.
Jones, P.B., Barnes, T.R., Davies, L., Dunn, G., Lloyd, H., Hayhurst, K.P., Murray, R.M., Markwick, A., Lewis, S.W., 2006. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch. Gen. Psychiatry 63, 1079–1087.
Kane, J.M., Sanchez, R., Perry, P.P., Jin, N., Johnson, B.R., Forbes, R.A., McQuade, R.D., Carson, W.H., Fleischhacker, W.W., 2012. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. J. Clin. Psychiatry 73, 617–624.
Kishimoto, T., Nitta, M., Borenstein, M., Kane, J.M., Correll, C.U., 2013. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J. Clin. Psychiatry 74, 957–965.
Lewis, S.W., Barnes, T.R., Davies, L., Murray, R.M., Dunn, G., Hayhurst, K.P., Markwick, A., Lloyd, H., Jones, P.B., 2006. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr. Bull. 32, 715–723.
Li, H., Rui, Q., Ning, X., Xu, H., Gu, N., 2011. A comparative study of paliperidone palmitate and risperidone long-acting injectable therapy in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 35, 1002–1008.
Lieberman, J.A., 2004. Dopamine partial agonists: a new class of antipsychotic. CNS Drugs 18, 251–267.
Lieberman, J.A., Jarskog, L.F., Malaspina, D., 2006. Preventing clinical deterioration in the course of schizophrenia: the potential for neuroprotection. J. Clin. Psychiatry 67, 983–990.
Nasrallah, H.A., Gopal, S., Gassmann-Mayer, C., Quiroz, J.A., Lim, P., Eerdekens, M., Yuen, E., Hough, D., 2010. A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia. Neuropsychopharmacology 35, 2072–2082.
Pandina, G., Lane, R., Gopal, S., Gassmann-Mayer, C., Hough, D., Remmerie, B., Simpson, G., 2011. A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 35, 218–226.
Perkins, D.O., 2002. Predictors of noncompliance in patients with schizophrenia. J. Clin. Psychiatry 63, 1121–1128.
Stahl, S.M., 2014. Long-acting injectable antipsychotics: shall the last be first? CNS Spectr. 19, 3–5.
Tandon, R., Devellis, R.F., Han, J., Li, H., Frangou, S., Dursun, S., Beuzen, J.N., Carson, W., Corey-Lisle, P.K., Falissard, B., Jody, D.N., Kujawa, M.J., L'italien, G., Marcus, R.N., McQuade, R.D., Ray, S., Van, P.P., 2005. Validation of the Investigator's Assessment Questionnaire, a new clinical tool for relative assessment of response to antipsychotics in patients with schizophrenia and schizoaffective disorder. Psychiatry Res. 136, 211–221.
Taylor, D., Hanssens, L., Loze, J.Y., Pans, M., L'italien, G., Marcus, R.N., 2008. Preference of medicine and patient-reported quality of life in community-treated schizophrenic patients receiving aripiprazole vs standard of care: results from the STAR study. Eur. Psychiatry 23, 336–343.
Thwin, S.S., Hermes, E., Lew, R., Barnett, P., Liang, M., Valley, D., Rosenheck, R., 2013. Assessment of the minimum clinically important difference in quality of life in schizophrenia measured by the Quality of Well-Being Scale and disease-specific measures. Psychiatry Res. 209, 291–296.
Tiihonen, J., Haukka, J., Taylor, M., Haddad, P.M., Patel, M.X., Korhonen, P., 2011. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am. J. Psychiatry 168, 603–609.
Wiens, B.L., 2002. Choosing an equivalence limit for noninferiority or equivalence studies. Control. Clin. Trials 23, 2–14.