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Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: A 12-month, double-blind, noninferiority study☆,☆☆,★

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ABSTRACT

Objective: To evaluate the relapse prevention efficacy of lurasidone compared with quetiapine XR (QXR) in adults patients with schizophrenia.
Method: This double-blind study evaluated the relapse prevention efficacy of 12 months of flexible-dose treatment with lurasidone (40–160 mg/day) compared with QXR (200–800 mg/day), in outpatients with an acute exacerbation of chronic schizophrenia who had recently completed a 6-week placebo-controlled trial of treatment with either lurasidone or QXR. The primary endpoint, time-to-relapse, was analyzed using a Cox proportional hazards model in this noninferiority trial.
Results: The Kaplan–Meier estimate of the probability of relapse over 12 months was 23.7% for subjects receiving lurasidone vs. 33.6% for QXR. The hazard ratio [95% CI] for probability of relapse was 0.728 [0.410, 1.295] (log-rank $p = 0.280$). Since the upper limit of the hazard ratio (1.295) was smaller than the prespecified noninferiority margin (1.93), noninferiority of lurasidone compared with QXR was demonstrated in this study. The probability of hospitalization at 12 months was lower for the lurasidone group compared with the QXR group (9.8% vs. 23.1%; log-rank $p = 0.049$). A significantly higher proportion of lurasidone subjects achieved remission at study endpoint compared with the QXR group (61.9% vs. 46.3%; $p = 0.043$). Discontinuation rates due to AEs were similar for lurasidone and QXR (7% vs. 5%). Treatment with lurasidone was not associated with clinically significant changes in weight or metabolic parameters.
Conclusions: Twelve months of treatment with lurasidone met noninferiority criteria, and was associated with higher rates of remission, and reduced risk of hospitalization compared with QXR. No clinically significant effects on weight or metabolic parameters were observed during maintenance treatment with lurasidone.

Lurasidone is an atypical antipsychotic agent with potent binding affinity for D_2, 5-HT_{2A}, and 5-HT_7 receptors, and moderate affinity for 5-HT_{1A} and α_{2C} receptors (Ishibashi et al., 2010). It has minimal affinity for histamine H_1 and muscarinic M_1 receptors, which are thought to contribute to side effects such as weight gain, sedation, and cognitive impairment (Ishibashi et al., 2010).

in the treatment
ura et al., 2009; Citrome, 2011; Meltzer et al., 2011). Evidence from both open-label continuation trials (Citrome, 2011; Stahl et al., in press), and a randomized, double-blind, long-term trial (Citrome et al., 2012), suggests that efficacy is maintained over a 12 month treatment period with a low potential for adverse effects on weight and metabolic parameters, thus making it a promising candidate for maintenance treatment.

We report here the results of a double-blind, 12 month follow-on study that utilized a noninferiority design to evaluate the relapse prevention efficacy of lurasidone versus quetiapine XR (QXR) in subjects who were responders to these treatments in an initial 6-week study. Use of a noninferiority design permitted a rigorous comparison of lurasidone with an established, well-tolerated agent, QXR, that is widely used, and which has received regulatory approval in the US and Europe for the maintenance treatment of schizophrenia based, in part, on demonstration of relapse prevention efficacy in a double-blind, randomized withdrawal study (Peuskens et al., 2007). The primary noninferiority comparison

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was time-to-relapse of psychotic symptoms for subjects treated with lurasidone and QXR.

2. Methods

This was a double-blind, parallel-group study, utilizing a previously randomized study population and a noninferiority design, to evaluate the relapse prevention efficacy of 12 months of flexible dose treatment with lurasidone (40–160 mg/d), compared with QXR (200–800 mg/d), in outpatients with an acute exacerbation of chronic schizophrenia who had recently completed 6 weeks of double-blind, placebo-controlled, fixed dose treatment with either lurasidone (80 mg/d or 160 mg/d) or QXR (600 mg/d, included to confirm assay sensitivity). The results of the preceding short-term efficacy study have been reported elsewhere (Loebel et al., 2013).

The study protocol was approved by Independent Review Boards or Ethics Committees associated with each study center, and all subjects provided separate written informed consent for this 12 month continuation study, which was conducted from December 2008 to June 2011 at 58 centers in 6 countries. The current long-term continuation study, as well as the preceding acute study phase was monitored by an independent Data and Safety Monitoring Board.

The primary relapse prevention analysis population was defined, a priori, as all subjects who were randomized to either once-daily lurasidone (80 mg or 160 mg) or QXR 600 mg in the initial 6 week treatment study, and who met clinical response criteria on Day 42, defined as ≥20% reduction in PANSS total score from acute study baseline and a CGI-S ≤ 4 at Day 42 (moderate-or-less illness severity). The core phase placebo to continuation lurasidone treatment group (PBO-LUR) was included in secondary efficacy and safety analyses. Study medication was taken once daily in the evening with a meal or within 30 min after eating.

2.1. Assessments

Efficacy was assessed using the PANSS total and subscale scores (Kay et al., 1994; Marder et al., 1997), the Clinical Global Impression, Severity scale (CGI-S; Guy, 1976), the Negative Symptom Assessment Scale (NSA-16; Axelrod et al., 1993), and the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979). PANSS and CGI-S evaluations were performed at Baseline (Day 42 of acute treatment), and at Months 3, 6, 9, and 12. The present study also included an assessment of cognitive function using a computerized cognitive battery (reported elsewhere; Harvey et al., 2012).

Safety evaluations included vital signs, laboratory tests, 12-lead ECG, and adverse events. Extrapyramidal symptoms were assessed with the Simpson–Angus Rating Scale (SAS; Simpson and Angus, 1970), the Barnes Rating Scale for Drug-Induced Akathisia (BAS; Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976). Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (Johns, 1991). Adherence was assessed by monthly counts of study medication; subjects who varied by more than 25% from their prescribed dose were considered noncompliant.

2.2. Statistical methods

The primary relapse analysis was a noninferiority comparison, based on a Cox proportional-hazards model (Cox, 1972), of time to relapse of psychotic symptoms in the subgroup of subjects who were responders to acute treatment and who continued to receive lurasidone (N = 139) and quetiapine XR (N = 79). Country was used as a covariate in the analysis. Relapse of psychotic symptoms was defined as the earliest occurrence of any of the following 3 criteria: (1) worsening of ≥30% in the PANSS total score from Day 42 of the initial acute treatment study and a CGI-S ≥ 3; (2) re-hospitalization for worsening of psychosis; or (3) emergence of suicidal ideation, homicidal ideation and/or risk of harm. Subjects were not unblinded at the time any relapse or hospitalization occurred.

Lurasidone was to be declared non-inferior to QXR in preventing relapse if the upper bound of the 2-sided 95% confidence limit for the hazard ratio of lurasidone versus QXR was no greater than a prespecified noninferiority margin of 1.93 (Leucht et al., 2003; Piaggio et al., 2006). Determination of this margin was based on a meta-analysis of relapse prevention studies in schizophrenia with second generation antipsychotics (SGAs) and placebo, which reported relapse rates as 19% and 49%, respectively, or a 30% difference between SGA and placebo (Leucht et al., 2003). In order to preserve at least 50% of the relapse prevention effect of SGAs compared to placebo, a noninferiority (NI) difference of 15% was selected and relapse rates of 35% for lurasidone and 20% for QXR were assumed (Piaggio et al., 2006; Peuskens et al., 2007).

Analysis of change in PANSS total and subscores, CGI-S, MADRS, and NSA-16 was made based on a mixed model for repeated measurement (MMRM) analysis that included fixed effects terms for treatment, visit (as a categorical variable), center, Day 0 score in the initial acute treatment study, and treatment-by-visit interaction (Liang and Zeger, 2000).

Remission rates during study treatment were assessed using the Remission in Schizophrenia Working Group (RSWG) criteria for symptomatic remission which require that a threshold of improvement be maintained for at least 6 months (Andreasen et al., 2005).

3. Results

Of the 353 subjects who completed the initial 6 week double-blind trial, 292 (83%) entered the current 12 month relapse prevention study: 151 subjects continued on lurasidone, 85 subjects continued on QXR, and 56 subjects treated with placebo in the initial trial were started on lurasidone (PBO-LUR group; Table 1). Subjects entering the initial 6 week study were hospitalized with an acute exacerbation of schizophrenia, with a mean PANSS total score at pre-treatment baseline of approximately 97 (Table 1). For the full intent-to-treat population in the core 6 week treatment study, significant efficacy was demonstrated for both the lurasidone and QXR treatment groups when compared with placebo on both the primary and key secondary efficacy outcomes (Loebel et al., 2013). At the completion of 6 weeks of treatment, the mean improvement in the PANSS total score was similar in the treatment groups that were continued on lurasidone and QXR (−30.0 vs. −29.2; p = 0.593; MMRM); and the mean improvement in CGI-S was also similar in the lurasidone and QXR treatment groups (−1.9 vs. −1.8; p = 0.259; MMRM). Fig. 1 summarizes patients' disposition during the 12 month course of the study.

3.1. Dose

During 12 months of lurasidone treatment, 4/151 (2.6%) subjects received a modal daily dose of 40 mg, 18/151 (11.9%) received a modal daily dose of 80 mg, 87/151 (57.6%) received a modal daily dose of 120 mg, and 42/151 (27.8%) received a modal daily dose of 160 mg.

During 12 months of QXR treatment, 1/85 (1.2%) subject received a modal daily dose of 200 mg, 9/85 (10.6%) received a modal daily dose of 400 mg, 48/85 (56.5%) received a modal daily dose of 600 mg, and 27/85 (31.8%) received a modal daily dose of 800 mg.

3.1.1. Efficacy

The Kaplan–Meier (KM) estimates of the probability of relapse at 12 months were 23.7% for the lurasidone group and 33.6% for the QXR group (Fig. 2-A). Subjects in the lurasidone group had a lower risk of relapse during 12 months of treatment compared with subjects in the QXR group, with a hazard ratio [95% CI] of 0.728 [0.410, 1.295], indicating a 27.2% reduction in relapse risk (primary, a priori Cox proportional hazards model analysis). Since the upper limit of the hazard ratio (1.295) was smaller than the prespecified noninferiority margin (1.93), the

Table 1
Baseline characteristics of subjects enrolled in the 12-month, double-blind, relapse prevention study comparing lurasidone and quetiapine XR.[a]

Characteristic	Lurasidone–lurasidone[b] (N = 151)		Quetiapine XR–quetiapine XR[b] (N = 85)		Placebo–lurasidone[b] (N = 56)	
	N	%	N	%	N	%
Male	108	72	52	61	35	63
Race						
White	87	58	56	66	32	57
Black	22	15	13	15	8	14
Asian	35	23	12	14	16	29
Other	7	5	4	5	0	0
Ethnicity, Hispanic/Latino	11	7	7	8	5	9
Prior hospitalizations: ≥4	71	47	41	48	26	46
	Mean	SD	Mean	Mean	Mean	SD
Age, years	37.1	11.7	38.5	10.4	37.5	11.4
Age at onset of illness, years	25.8	8.6	24.9	8.2	26.1	9.3
Duration of illness, years	10.8	9.4	13.2	10.3	11.0	9.7
Duration of current episode, days	31.4	12.0	30.6	11.8	34.7	14.6
PANSS Total score[c]						
Acute baseline	97.7	10.3	97.9	10.6	96.4	10.6
12-month baseline	66.7	15.5	67.8	14.2	76.3	17.2
CGI-Severity[c]						
Acute baseline	4.9	0.5	4.9	0.6	5.0	0.4
12-month baseline	3.0	0.7	3.1	0.8	3.7	0.8
MADRS total score[c]						
Acute baseline	12.0	8.1	12.8	8.8	11.1	6.6
12-month baseline	5.7	4.9	7.0	5.6	7.1	5.6

PANSS = Positive and Negative Syndrome Scale; CGI = Clinical Global Impressions scale; MADRS = Montgomery–Åsberg Depression Rating Scale.
[a] Data shown are for the safety population, except for PANSS total, CGI-Severity and MADRS scores, which are based on the intent-to-treat population.
[b] Lurasidone–lurasidone: treated with lurasidone in both the acute double-blind and maintenance studies; placebo–lurasidone: treated with lurasidone in the acute double-blind study, then switched to lurasidone in the maintenance study; quetiapine XR–quetiapine XR: treated with quetiapine XR in both the core double-blind and maintenance studies.
[c] Based on ITT population (lurasidone–lurasidone, n = 132; quetiapine XR–quetiapine-XR, n = 72; placebo–lurasidone, n = 52).

noninferiority of lurasidone compared with QXR was demonstrated in this study.

The KM estimate of the probability of hospitalization at 12 months was significantly lower for lurasidone vs. QXR (9.8% vs. 23.1%; $p < 0.05$; Fig. 2-B). Twelve months of treatment with lurasidone was associated with a 56.7% reduction in the risk of hospitalization compared with QXR (hazard ratio [95% CI], 0.433 [0.188, 0.995]; based on a post-hoc Cox proportional hazards model). The rate of hospitalization among subjects who met a priori relapse criteria was significantly higher for QXR (61.9%) compared with lurasidone (34.5%; $p < 0.05$).

A sensitivity analysis was performed for all subjects who continued treatment with lurasidone (n = 151) or QXR (n = 85) in the current study regardless of responder status. A lower probability of relapse at 12 months for lurasidone vs. QXR (23.0% vs. 35.8%; hazard ratio [95% CI] of 0.660 [0.381, 1.143] was found; Supplemental Fig. S1).

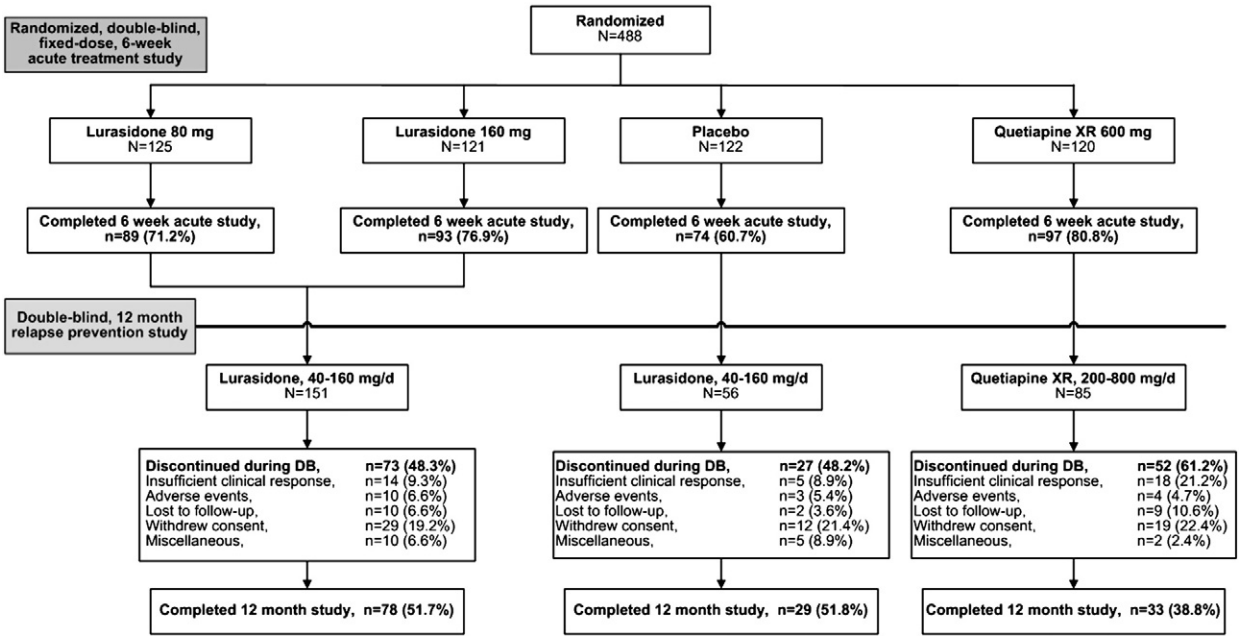

Fig. 1. Study flow diagram and subject disposition during 12 months of double-blind (DB) treatment with lurasidone or quetiapine XR in the relapse prevention study.

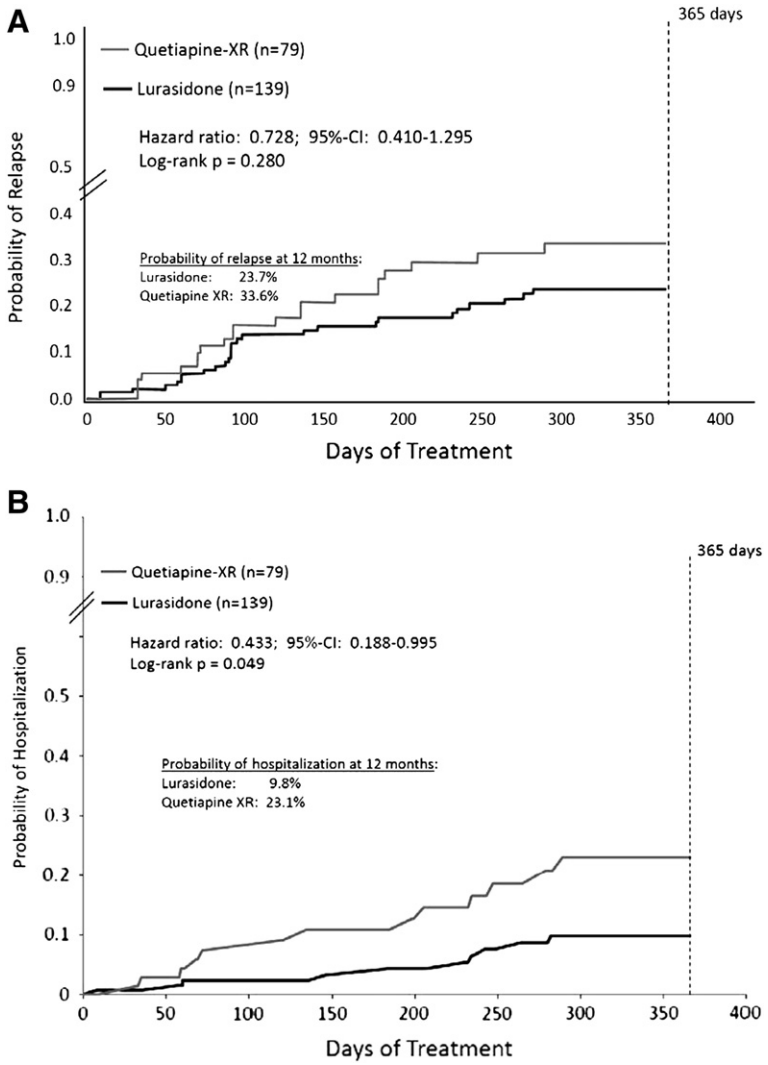

Fig. 2. Kaplan–Meier plots. A. Probability of not relapsing during 12 months of double-blind treatment with lurasidone (LUR–LUR) or quetiapine XR (QXR–QXR) during the relapse prevention study. B. Probability of not being hospitalized during 12 months of double-blind treatment with lurasidone (LUR–LUR) or quetiapine XR (QXR–QXR) in the relapse prevention study.

3.1.2. Secondary efficacy analyses

There was significantly greater change in the PANSS total and positive subscale scores for lurasidone vs. QXR (Table 2; Supplemental Fig. S2), however, endpoint improvement was similar for the PANSS negative subscale, NSA-16, and CGI-S scores (Table 2). Among subjects in the PBO-LUR group, endpoint improvement in PANSS total and subscale scores, CGI-S, and MADRS was comparable to that observed for subjects initially treated with lurasidone (Supplemental Table S1).

A significantly higher proportion of subjects met full RSWG remission criteria (including the minimum 6-month duration criterion) (Andreasen et al., 2005), in the lurasidone group compared with the QXR group (61.9% vs. 46.3%; $p < 0.05$; LOCF endpoint analysis).

There was significantly greater change in the MADRS, from pre-treatment baseline for subjects who continued treatment with lurasidone compared with subjects who continued treatment with QXR (-6.0 vs. -3.8; $p < 0.05$; Supplemental Fig. S3), but not from the baseline of the current 12 month study (Table 2).

3.1.2.1. Safety. The effect of study treatment on safety parameters (laboratory values, weight) is reported using an OC analysis of change from pre-treatment baseline (Table 3).

3.1.2.2. Body weight, BMI, and waist circumference. There were minimal effects on mean body weight, BMI, and waist circumference in the lurasidone and PBO-LUR groups (OC analysis of change from acute study baseline; Table 3). Clinically significant ($\geq 7\%$) increase in weight, from acute study baseline, was reported by a lower proportion of subjects at Months 6 and 12 in the lurasidone group (13.6% and 11.5%, respectively), and the PBO-LUR group (10.3% and 13.8%) compared with the QXR group (27.5% and 15.2%; Table 3).

3.1.2.3. Metabolic parameters. As summarized in Table 3, 12 months of treatment with lurasidone and QXR was associated with minimal effects on lipid parameters and measures of glycemic control, including glucose, HbA1c, insulin, and HOMA-IR. At Month 6, treatment with QXR was associated with an increase in total and LDL cholesterol, and triglycerides, but minimal changes were observed among completers at Month 12.

3.1.2.4. Prolactin and other laboratory values. The median changes in prolactin levels at Months 6 and 12 were similar among subjects in the lurasidone, QXR, and PBO-LUR groups (Table 3). No clinically relevant differences were noted for any other laboratory values when comparing the lurasidone, QXR, and PBO-LUR groups.

Table 2
Efficacy measures after 12 months of double-blind treatment in the relapse prevention study: LS mean change from the baseline of the 6 week acute and 12 month relapse prevention studies.

Measure	Lurasidone–lurasidone (n = 132)		Quetiapine XR–quetiapine XR (n = 72)	
	LS Mean	SE	LS Mean	SE
PANSS				
Total				
Change from acute study baseline	−34.6**	1.8	−25.7	2.6
Change from 12-month study baseline	−5.0**	1.4	+1.7	2.1
Positive subscale				
Change from acute study baseline	−12.3**	0.5	−9.6	0.7
Change from 12-month study baseline	−1.5**	0.4	+0.7	0.6
Negative subscale				
Change from acute study baseline	−7.2	0.4	−6.6	0.6
Change from 12-month study baseline	−0.9	0.4	−0.8	0.5
CGI-S				
Change from acute study baseline	−1.9	0.1	−1.6	0.1
Change from 12-month study baseline	0.0	0.1	+0.2	0.1
NSA-16				
Change from acute study baseline	−14.7	0.8	−15.0	1.1
Change from 12-month study baseline	−3.7	0.8	−4.3	1.1
MADRS				
Change from acute study baseline	−6.0*	0.6	−3.8	0.9
Change from 12-month study baseline	+0.1	0.6	+1.3	0.8

*p < 0.05. **p < 0.01. ***p < 0.001.
PANSS: Positive and Negative Syndrome Scale; CGI-S: Clinical Global Impression, Severity Scale; MADRS: Montgomery–Asberg Depression Rating Scale; NSA-16: Negative Symptom Assessment Scale; LS: least squares; acute baseline: prior to randomization in the previous acute 6-week double-blind study; estimates, standard errors (SE), and p-values are based on a mixed model for repeated measures (MMRM) of the change from acute/maintenance baseline score; the analysis used fixed effects for pooled center, visit as a categorical variable, acute/maintenance baseline score, treatment, and treatment by visit interaction, and assumed an unstructured covariance matrix. The ITT sample for secondary efficacy analyses consisted of subjects who had both a baseline and at least one post-baseline efficacy assessment.

3.1.2.5. Physical examination and vital signs. Orthostatic hypotension occurred at some point during the overall course of the initial 6 week and 12 month follow-on studies in 3/203 (1.5%) subjects in the combined lurasidone group, and in 3/81 (3.7%) subjects in the QXR group; orthostatic tachycardia occurred in 3/203 (1.5%) of the subjects in the lurasidone group, and in 6/81 (7.4%) of the subjects in the QXR group. There were no other clinically significant treatment-emergent changes in either of the lurasidone groups or the QXR group in vital signs or physical examination.

3.1.2.6. ECG. There were no clinically significant treatment-emergent ECG abnormalities in the lurasidone, QXR, and PBO-LUR groups. The mean increases in QTcF interval, from acute study baseline to Month 12, were 5.8 ms in the lurasidone group (n = 76), 8.7 ms in the PBO-LUR group (n = 29), and 0.8 ms in the QXR group (n = 31). The mean increases in QTcF interval, from acute study baseline to Month 12, based on an LOCF analysis, were 4.3 ms in the lurasidone group (n = 122), 8.8 ms in the PBO-LUR group (n = 49), and 1.1 ms in the QXR group (n = 65). No subjects in any of the 3 treatment groups experienced ≥60 ms increase in QTcF interval, or had a QTcF interval >500 ms, at any time during 12 months of treatment in the current study.

3.1.2.7. Extrapyramidal symptoms and akathisia. The proportions of subjects reporting an extrapyramidal-related adverse event during 12 months of treatment in the current study were 11.9% in the lurasidone group, 3.5% in the QXR group, and 21.4% in the PBO-LUR group. The incidences of akathisia were 12.6% in the lurasidone group, 2.4% in the QXR group, and 10.7% in the PBO-LUR group. As summarized in Supplemental Table S2, there were minimal changes in the BAS, SAS, and AIMS during 12 months of study treatment. The proportions of subjects who received an anticholinergic medication at any time during 12 months of treatment in the current study were 19.2% in the lurasidone group, 5.9% in the QXR group, and 21.4% in the PBO-LUR group. Beta-adrenoceptor blocking agents were used by 4.6% of subjects in the lurasidone group, 5.9% of subjects in the QXR group, and 5.4% of subjects in the PBO-LUR group.

3.1.2.8. Adverse events. The proportions of subjects reporting at least one adverse during 12 months of treatment in the current study were 64.2% for the lurasidone group, 62.5% for the PBO-LUR group, and 71.8% for the QXR group (Supplemental Table S3). The three most frequent adverse events in the lurasidone group were akathisia (12.6%), headache (10.6%), and insomnia (7.9%); and the three most frequent events in the QXR group were worsening of schizophrenia (15.3%), insomnia (9.4%), and headache (9.4%). The majority of adverse events in all treatment groups were rated as mild to moderate in intensity.

4. Discussion

We report here the results of a double-blind, long-term, follow-on study comparing the efficacy of flexibly-dosed lurasidone and QXR for the prevention of relapse in schizophrenia. A number of different study designs have been utilized to assess the maintenance efficacy of antipsychotic treatment in patients with schizophrenia. To our knowledge this is the first study to incorporate all of the following features: a double-blind, parallel group, continuation design, using prespecified relapse criteria and a non-inferiority analysis. These design features provide a methodologically rigorous basis for the assessment of the maintenance efficacy of lurasidone in the treatment of schizophrenia.

Lurasidone was found to be non-inferior to QXR in time-to-relapse, with a numerically lower probability of relapse at 12 months in the lurasidone group compared with the QXR group (23.7% vs. 33.6%; log-rank p = 0.280). A sensitivity analysis involving all subjects treated with lurasidone or QXR in the initial 6 week study (regardless of responder status) was consistent with the primary analysis: the probability of relapse at 12 months was lower in the lurasidone group compared with the QXR group (23.0% vs. 35.8%; log-rank p < 0.05).

Table 3
Safety parameters: change from acute study baseline to months 6 and 12 (observed case analysis).

	Lurasidone–lurasidone		Quetiapine XR–quetiapine XR		Placebo–lurasidone	
	n		n		n	
Weight, kg, mean (SD)						
Baseline, acute study	151	72.7 (15.8)	85	72.4 (17.4)	56	73.9 (16.5)
Month 6 change	103	+1.3 (4.0)	51	+2.4 (6.3)	39	+0.4 (4.6)
Month 12 change	78	+0.7 (3.4)	33	+1.2 (4.6)	29	+0.3 (4.9)
≥7% increase in weight, n (%)						
Month 6 change	103	14 (13.6)	51	14 (27.5)	39	4 (10.3)
Month 12 change	78	9 (11.5)	33	5 (15.2)	29	4 (13.8)
Body mass index, kg/m^2, mean (SD)						
Baseline, acute study	151	25.0 (4.5)	85	25.6 (4.9)	56	25.7 (4.9)
Month 6 change	103	+0.5 (1.4)	51	+0.8 (2.1)	39	+0.1 (1.6)
Month 12 change	78	+0.3 (1.2)	33	+0.5 (1.6)	29	+0.1 (1.7)
Waist circumference, cm, mean (SD)						
Baseline, acute study	151	86.3 (13.2)	85	87.2 (14.4)	56	86.8 (12.9)
Month 6 change	103	+1.4 (5.0)	51	+1.2 (8.4)	39	+0.2 (6.7)
Month 12 change	78	+0.9 (3.8)	33	+0.6 (4.3)	29	+1.6 (5.7)
Total cholesterol, mg/dL, median						
Baseline, acute study	151	184.0	85	187.0	56	183.5
Month 6 change score	102	−7.0	51	+6.0	39	−17.0
Month 12 change score	77	0.0	33	+4.0	28	−11.5
LDL cholesterol, mg/dL, median						
Baseline, acute study	151	111.0	85	109.0	56	109.0
Month 6 change score	102	−1.5	51	+4.0	39	−8.0
Month 12 change score	77	−3.0	33	0.0	28	−5.0
HDL cholesterol, mg/dL, median						
Baseline, acute study	151	44.0	85	42.0	56	42.0
Month 6 change score	102	0.0	51	0.0	39	−4.0
Month 12 change score	77	0.0	33	+4.0	28	−4.0
Triglycerides, mg/dL, median						
Baseline, acute study	151	106.0	85	112.0	56	120.0
Month 6 change	102	0.0	51	+6.0	39	−15.0
Month 12 change	77	−18.0	33	−7.0	28	−17.5
Glucose, mg/dL, median						
Baseline, acute study	151	92.0	85	91.0	56	92.5
Month 6 change	100	−0.5	50	+2.0	39	−4.0
Month 12 change	76	+1.0	33	+1.0	28	−2.5
HbA1c, %, mean						
Baseline, acute study	151	5.5	85	5.5	56	5.4
Month 6 change	98	+0.1	46	+0.0	36	+0.1
Month 12 change	76	+0.2	33	+0.0	29	+0.1
Insulin, mU/L, median						
Baseline, acute study	148	9.2	82	8.7	56	9.1
Month 6 change	98	−1.8	49	−2.0	39	−2.8
Month 12 change	76	−0.9	32	+1.2	28	+0.6
HOMA-IR, mean						
Baseline, acute study	146	4.4	82	4.0	55	3.7
Month 6 change	95	−1.8	48	−1.4	39	−0.6
Month 12 change	75	−1.8	32	+0.2	28	−1.3
Prolactin, ng/mL, median						
Baseline, acute study	151	7.9	85	8.7	56	9.4
Month 6 change	102	0.0	51	−1.3	39	+1.0
Month 12 change	77	+0.6	33	−0.7	28	+1.0

Month 6: 6 months post-baseline of relapse prevention study; Month 12: 12 months post-baseline of relapse prevention study.
HbA1c = glycosylated hemoglobin; HOMA-IR = homeostatic model assessment of insulin resistance (analyzed post hoc); LDL = low-density lipoprotein; HDL = high-density lipoprotein.

For the population included in the primary analysis, the probability of hospitalization at 12 months (one component of the prespecified composite relapse risk definition) was lower for the lurasidone group compared with the QXR group (9.8% vs. 23.1%; log-rank $p < 0.05$). In addition, the rate of hospitalization was higher among subjects who relapsed and who were treated with QXR (61.9%) compared with lurasidone (34.5%; $p < 0.05$). These results suggest that psychotic relapse was not only more frequent, but may have been associated with greater severity in patients treated with QXR. Since hospitalization accounts for the largest share of the cost of schizophrenia (Ascher-Svanum et al., 2010; Peng et al., 2011), reduction in risk of hospitalization is likely to be associated with substantial cost savings. An analysis of the estimated cost savings associated with lurasidone treatment in this study will be reported separately.

The major findings of the current study should be placed in the context of previous relapse prevention trials. Two recent meta-analyses have evaluated the relapse prevention efficacy of antipsychotic drugs during the longer-term treatment of schizophrenia. In a meta-analysis of 65 placebo-controlled trials (Leucht et al., 2012), antipsychotic agents were found to significantly reduce relapse rates at 12 months when compared with placebo (antipsychotics 27% vs. placebo 64%; risk ratio [RR] 0.40). In a meta-analysis of 26 randomized trials comparing atypical and conventional antipsychotics (Kishimoto et al., 2011), atypicals were found to significantly reduce relapse rates at 12 months when compared with conventional antipsychotics (atypicals, 31% vs. conventionals, 37%). These meta-analyses underscore the substantial efficacy of antipsychotic agents in maintaining improvement and preventing relapse in patients with schizophrenia.

The results of the current study suggest that lurasidone is associated with a relapse rate at one year (23.7%) that is comparable, or better than, the rate reported in meta-analyses of randomized trials comparing atypical (31%) and conventional antipsychotics (37%; Kishimoto et al., 2011), and is comparable to the rate reported at one year for antipsychotics in placebo-controlled trials (27%; Leucht et al., 2012). One randomized, double-blind study is available that specifically evaluated the relapse prevention efficacy of QXR over a 6 month duration (Peuskens et al., 2007). In that study, the relapse rate at 6 months was 14.3% for QXR, which was somewhat lower than the estimated rate (approximately 21%) observed at 6 months in the current 12 month trial (Fig. 2-A). The lower relapse rate at 6 months in the study by Peuskens et al. (2007) may be accounted for by differences in study design (4 month stabilization; randomized withdrawal design), and by inclusion of a less severely ill patient sample.

The comparative effectiveness of lurasidone in the long-term treatment of schizophrenia was also demonstrated on secondary measures in the current study. Discontinuation due to insufficient clinical response was lower in the lurasidone group compared with the QXR group (9.3% vs. 21.2%). Treatment with lurasidone was associated with significantly greater endpoint improvement versus QXR in the PANSS total and positive subscale; but was similar on the PANSS negative subscale and on the NSA-16.

Remission rates, based on full RSWG criteria requiring sustained improvement for at least 6 months (Andreasen et al., 2005), were also higher for the lurasidone group compared with the QXR group (61.9% vs. 46.3%; $p < 0.05$). The remission rate observed in the lurasidone treatment group is notable as the study population had experienced a recent acute exacerbation (mean PANSS total score at acute study baseline, 97) of a highly chronic, recurrent illness (mean duration > 10 years; approximately half of subjects with ≥4 prior hospitalizations), and had not experienced an extended, post-acute period of stabilization prior to entering the current study. Remission is an important treatment goal in schizophrenia because it is correlated with functional and occupational outcomes (Bodén et al., 2009; Cassidy et al., 2010). The remission rate observed for lurasidone in the current study is among the highest reported in studies that utilize full RSWG criteria to define remission (Emsley et al., 2011). The functional outcome implications of remission rate findings in the current study warrant further investigation.

The consistency of the efficacy advantage in favor of lurasidone in the current study is in contrast to the results of the initial 6 week, fixed dose, double-blind trial, where improvement on lurasidone and QXR was similar (Loebel et al., 2013). The reasons for emergence of an efficacy difference favoring lurasidone during this continuation study are uncertain. The difference in relapse risk does not appear to be due to a difference in tolerability between lurasidone and QXR, since discontinuation due to adverse events was similar in this continuation study (6.6% vs. 4.7%). The difference in relapse risk in favor of lurasidone also does not appear to be due to inadequate dosing with QXR, since the modal daily dose of QXR was either 600 mg or 800 mg in 88% of subjects. The mean modal daily dose of QXR utilized in the current study (637.6 mg) was similar to the mean dose of 646 mg used in a previous QXR relapse prevention study (Peuskens et al., 2010). Furthermore, daily dosages of QXR above 600 mg have not been shown to be associated with a significant efficacy advantage compared with a daily dose of 600 mg (Zhornitsky et al., 2011).

The results of the current study suggest that 12 months of treatment with lurasidone, in doses up to 160 mg/day, has a relatively low potential for causing adverse weight and metabolic effects. Triglyceride levels were reduced in the lurasidone group, while total and LDL cholesterol levels were either unchanged or reduced. Long-term treatment with lurasidone was also found to have no adverse effect on measures of glycemic control, as indicated by minimal effects on glucose, HbA1c, insulin, and HOMA-IR. These long-term data confirm and extend the findings obtained in short-term, fixed dose lurasidone studies (Nakamura et al., 2009; Citrome, 2011; Meltzer et al., 2011) indicating that lurasidone has a low propensity for adverse effects on weight, lipids and glucose metabolism. With evidence suggesting that cardiovascular mortality risk in schizophrenia may have increased since the introduction of atypical antipsychotics (Saha et al., 2007; Weinmann et al., 2009; Brown et al., 2010), there is little doubt that additional metabolically neutral antipsychotic treatment options are needed, in addition to close attention to physical health monitoring for patients receiving maintenance treatment (Meyer, 2010).

Treatment with QXR was associated with clinically significant increases in weight and metabolic parameters at 6 months, however, changes were minimal among the 39% of subjects who completed 12 months of treatment. The variation in weight and metabolic outcomes observed for QXR at 6 and 12 months of treatment in the current study may be attributable, in part, to relatively high attrition rates (61.2%) over 12 months of treatment with this agent. Treatment with QXR was also associated with small increases at 12 months in glucose, insulin, and HOMA-IR, but no change in HbA1c. These findings are consistent with changes in glycemic control reported in a previous long-term QXR study need reference here.

Overall, 12 months of treatment with lurasidone and QXR was generally well-tolerated, with the majority of adverse events in the mild-to-moderate severity range. Movement disorder-related adverse events were reported more frequently by lurasidone compared to QXR-treated subjects (11.9% vs.3.5%). The rates of parkinsonism (6.0%) and akathisia (12.6%) for lurasidone in the current study were consistent with previous trials in subjects with schizophrenia (Latuda USPI, 2012).

This was the first lurasidone long-term study to utilize evening dosing of study medications. The relatively low incidence of adverse events observed in both the preceding acute study (Loebel et al., 2013), and this 12-month continuation study, suggests that this may be an optimal dosing strategy for lurasidone.

Several potential study limitations should be noted. First, subjects did not undergo a prespecified period of stabilization prior to entry into the relapse prevention phase. Second, all subjects who completed the acute study were enrolled in the current 12 month relapse prevention study, but were not re-randomized at the time of entry. Re-randomization may have provided a more reliable method for limiting potential selection bias for each study group in this study. However, the similarity of baseline clinical and demographic variables in the core study and the current study, and the similarity in results for the primary analysis and a sensitivity analysis that included all subjects (regardless of responder status), suggest that selection bias may have been minimal. Third, the current study did not include a placebo control, which was judged to be ethically problematic in a 12 month trial in chronic schizophrenia.

In conclusion, this double-blind, active comparator-controlled, 12-month, flexible-dose study in patients with schizophrenia, demonstrated noninferiority to QXR for lurasidone in *relapse* prevention. In addition, 12 months of treatment with lurasidone was associated with a relatively low probability of relapse and hospitalization, and a relatively high remission rate. This study also supports lurasidone's low potential for long-term adverse effects on weight and other indices of metabolic function. This study also suggests that long-term noninferiority studies using an active comparator are feasible in patients with schizophrenia, and have the potential to show clinical differentiation among antipsychotic agents.

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Contributors

Drs. Loebel, Cucchiaro, Sarma, Xu, Sarma, Pikalov, and Kane contributed to the analysis and interpretation of the data, and the writing and revision of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Drs. Loebel, Cucchiaro, Xu, Sarma, Pikalov, and Sarma are employees of Sunovion Pharmaceuticals.

Dr. Kane has been a consultant to Astra-Zeneca, Janssen, Pfizer, Eli Lilly, Bristol-Myers Squibb, Dainippon Sumitomo/Sepracor/Sunovion, Johnson & Johnson, Otsuka, Vanda, Proteus, Takeda, Targacept, IntraCellular Therapies, Merck, Lundbeck, Novartis Roche, Rules Based Medicine, Sunovion, Alkermes, Amgen, and Pierre Fabre, and has received honoraria for lectures from Otsuka, Eli Lilly, Bristol-Myers Squibb, Merck, and Janssen. He is a shareholder of MedAvante. He has received grant support from The National Institute of Mental Health.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.03.013.

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