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Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: A randomized, double-blind, placebo- and active-controlled trial ☆

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ABSTRACT

Objective: This study was designed to evaluate the short-term efficacy and safety of once-daily lurasidone (80 mg/day and 160 mg/day) in the treatment of an acute exacerbation of schizophrenia.
Methods: Participants, who were recently admitted inpatients with schizophrenia with an acute exacerbation of psychotic symptoms, were randomly assigned to 6 weeks of fixed-dose, double-blind treatment with lurasidone 80 mg (n = 125), lurasidone 160 mg (n = 121), quetiapine XR 600 mg (QXR-600 mg; n = 119; active control included to test for assay sensitivity), or placebo (n = 121), all dosed once daily in the evening. Efficacy was evaluated using a mixed-model repeated-measures analysis of the change from Baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) total score (the primary efficacy measure) and Clinical Global Impressions severity (CGI-S) score (the key secondary efficacy measure).
Results: Treatment with both doses of lurasidone or with QXR-600 mg was associated with significantly greater improvement at Week 6 on PANSS total score, PANSS positive and negative subscale scores, and CGI-S score compared with placebo. The endpoint responder rate (≥20% improvement in PANSS total score) was higher in subjects treated with lurasidone 80 mg (65%; $p<0.001$), lurasidone 160 mg (79%; $p<0.001$), and QXR-600 mg (79%; $p<0.001$) compared with placebo (41%). The proportion of patients experiencing ≥7% weight gain was 4% for each lurasidone group, 15% for the QXR-600 mg group, and 3% for the placebo group. Endpoint changes in levels of cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol were comparable for both lurasidone groups and placebo, while the QXR-600 mg group showed a significant median increase compared with the placebo group in levels of cholesterol ($p<0.001$), LDL cholesterol ($p<0.01$), and triglycerides ($p<0.05$).
Conclusions: Lurasidone 80 mg and 160 mg doses administered once-daily in the evening, were safe and effective treatments for subjects with acute schizophrenia, with increased response rates observed at the higher dose. Dose-related adverse effects were limited, and both doses were generally well-tolerated.

1. Introduction

Lurasidone hydrochloride (HCl) is a novel benzisothiazol derivative that has recently been approved by the FDA for the treatment of schizophrenia. Lurasidone has potent binding affinity for D_2, 5-HT_{2A} and $5HT_7$ receptors (antagonist effect), moderate affinity for $5HT_{1A}$ (partial agonist effect) and α_{2C} receptors (antagonist effect), and no appreciable affinity for H_1 and M_1 receptors (Ishibashi et al., 2010).

The efficacy of lurasidone, in once-daily doses ranging from 40 to 120 mg, in the treatment of acute exacerbations of schizophrenia has been demonstrated in previous double-blind, placebo-controlled studies (Nakamura et al., 2009; Citrome, 2011; Meltzer et al., 2011; Ogasa et al., 2013). Since lurasidone doses above 120 mg/d have not been previously studied in any placebo-controlled clinical trial, it is unclear whether doses above 120 mg/d have utility in the treatment of schizophrenia.

Empirically establishing the full therapeutic dosing range for new antipsychotic agents has proven to be challenging. Examination of atypical antipsychotic dosing patterns over time suggests that dose ranges ultimately judged to be optimal in the "real world" may differ from initial recommendations based on the results of registration

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trials (Citrome et al., 2005; Cutler et al., 2008; Kinon et al., 2008; Citrome et al., 2009). Although the specific reasons for such gradual evolution in dosage patterns are not clear, clinical trials may include subjects with somewhat less diagnostic heterogeneity, comorbidity and illness severity than patients encountered in clinical practice settings (Seeman, 2001). In addition, since D_2 receptor occupancy rates show a significant degree of inter-individual variability at a given dose (Kapur et al., 2000; Mamo et al., 2004; Catafau et al., 2009), higher daily doses may be required in some patients to ensure that adequate steady-state plasma and CNS concentrations are reached. From a practical standpoint, dose escalation is one of the most frequently used treatment strategies for patients with more severe illness and those who do not respond to initial treatment at lower therapeutic doses (Kinon et al., 2004; Schwartz and Stahl, 2011).

This is the first placebo-controlled trial to evaluate the efficacy and safety of treatment with lurasidone 160 mg/d, a dose above the previously established therapeutic range. The study utilized a fixed-dose design that included a lurasidone 80 mg arm (to permit assessment of dose–response effects) and a quetiapine XR arm (QXR-600 mg), to establish assay sensitivity.

2. Methods

This was a multiregional, prospective, parallel-group study in which subjects with a primary diagnosis of schizophrenia, who had been recently hospitalized for an acute exacerbation of psychotic symptoms, were randomly assigned to receive 6 weeks of double-blind treatment with once-daily evening doses of lurasidone (80 mg, 160 mg), QXR (600 mg), or placebo. The study was conducted between October 21, 2008, and June 2, 2010, enrolling a total of 486 subjects at 24 centers in the United States (n = 151 subjects), 10 centers in Russia (n = 87), 10 centers in India (n = 98), 9 centers in Ukraine (n = 75), 6 centers in Romania (n = 49), and 4 centers in Colombia (n = 26). Subjects who successfully completed this 6-week trial were eligible for enrollment in a 12-month double-blind extension study.

All subjects who entered the trial reviewed and provided informed consent. The study protocol was approved by an independent ethics committee associated with each study center. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practices guidelines and with the ethical principles of the Declaration of Helsinki. An independent data and safety monitoring board reviewed safety and clinical outcome data at regular intervals during the study.

2.1. Entry criteria

Hospitalized male and female subjects 18–75 years of age, inclusive, who met DSM-IV-TR criteria for a primary diagnosis of schizophrenia as determined by clinical interview using the Mini International Neuropsychiatric Interview Plus (Sheehan et al., 1998) were enrolled. Subjects were also required to have an illness duration greater than 1 year with the current acute exacerbation of psychotic symptoms no longer than 2 months and, at the Screening and Baseline visits, to have a Clinical Global Impression, Severity (CGI-S) score ≥4 (moderate or greater) and a Positive and Negative Syndrome Scale (PANSS) total score ≥80, including a score ≥4 (moderate) on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness.

2.2. Study medication

All study medication was identically overencapsulated to preserve the double-blind. After completing a Screening period (≤14 days) during which they were tapered off psychotropic medication, subjects completed a 3- to 7-day placebo washout period. At Baseline (day 0), subjects were randomly assigned (in a 1:1:1:1 ratio) via an interactive voice response system to one of four treatment arms: lurasidone, 80 mg/day; lurasidone, 160 mg/day; QXR, 600 mg/day; or placebo. Study medication was administered in the evening with a meal or within 30 min after eating. Subjects assigned to lurasidone 80 mg/day started treatment at their target dose. Subjects assigned to lurasidone 160 mg/day started treatment at a dose of 120 mg/day for 2 days before being increased to their target dose. Subjects assigned to QXR 600 mg/day were started at a dose of 300 mg/day for 2 days before being increased to their target dose (consistent with manufacturer recommendations). The QXR dosage of 600 mg/day was selected because it has been established as an effective dose in the middle of the approved dosing range for the treatment of patients with schizophrenia (Seroquel XR USPI), and because there does not appear to be a significant efficacy advantage when using the highest approved 800 mg dose (Kahn et al., 2007; Lindenmayer et al., 2011; Zhornitsky et al., 2011).

Subjects were eligible for hospital discharge after completing 21 days of double-blind treatment if they met specific clinical stability criteria.

2.3. Assessments

The screening evaluation consisted of the Mini International Neuropsychiatric Interview Plus (Sheehan et al., 1998), medical and psychiatric histories, a physical examination, measurement of vital signs, ECG, and laboratory tests. Efficacy was assessed using the PANSS total and subscale scores (Kay et al., 1987; Marder et al., 1997), the CGI-S (Guy, 1976), the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979), the Negative Symptom Assessment Scale (NSA-16; Axelrod et al., 1993), an interviewer administered version of the Quality of Well-being Scale (QWB-SA; Kaplan et al., 1998); and the single-item, subject-rated Medication Satisfaction Questionnaire (MSQ; Vernon et al., 2010). The subject-rated, 8-item Epworth Sleepiness Scale was administered at Baseline, and Weeks 3 and 6 to evaluate the level of daytime sleepiness.

Safety evaluations included vital signs, weight, body mass index, waist circumference, laboratory tests (including lipids, glucose, glycosylated hemoglobin [HbA1c], insulin, and prolactin, C-reactive protein), 12-lead ECG, and subject-reported adverse events. Extrapyramidal symptoms were assessed with the Simpson-Angus Rating Scale (Simpson and Angus, 1970), the Barnes Rating Scale for Drug-Induced Akathisia (Barnes, 1989), and the Abnormal Involuntary Movement Scale (Guy, 1976).

The present study also included an assessment of the effects of treatment on cognitive function using a computerized cognitive battery (CogState; Pietrzak et al., 2009). Cognitive assessment findings from this study will be reported elsewhere (Harvey et al., 2011).

2.4. Statistical methods

The study was powered at 97.5% to detect an 8-point difference with a pooled standard deviation of 19 between lurasidone and placebo in Week 6 change-from-baseline in PANSS total scores and reject the null hypothesis of no difference from placebo in at least one lurasidone dose at an α-level of 0.05 based on a 2-sided test.

The primary efficacy measure was the change from Baseline in PANSS total score at Week 6, and the key secondary efficacy measure was the change from Baseline in CGI-S score at Week 6. Both measures were evaluated by a mixed-model repeated-measures (MMRM) analysis with an unstructured covariance matrix, as used in a previously reported clinical trial (Meltzer et al., 2011). The p-values for the comparison of each lurasidone group with the placebo group at Week 6 on changes from Baseline in PANSS total score and in CGI-S score were adjusted for multiple comparisons using the Hommel-based tree-gatekeeping procedure. The QXR-600 mg treatment group was compared with placebo using the same mixed-model repeated measures model, without adjustment

for multiplicity for the comparison with placebo. A prespecified secondary analysis was also conducted for change in PANSS total score and CGI-S score at Week 6 LOCF endpoint, using an analysis of covariance (ANCOVA) model, with effects for Baseline score, pooled center, and treatment.

The PANSS responder rates (defined a priori as ≥20% improvement in PANSS total score) were evaluated with logistic regression using responder outcome as the dependent variable, treatment as a categorical factor, and Baseline PANSS total score as a covariate.

The PANSS subscores and symptom factor scores were evaluated using MMRM and a supportive ANCOVA. MADRS, NSA-16, and QWB-SA were evaluated using ANCOVA. There was no adjustment for multiplicity for these parameters.

Significance testing of safety parameters was performed based on a nonparametric rank ANCOVA with Baseline value as a covariate, not adjusted for multiple comparisons.

3. Results

A total of 668 subjects were screened and entered the washout period, of whom 488 were randomly assigned to 6 weeks of double-blind treatment (Fig. 1). Baseline demographic and clinical characteristics were comparable among the four treatment groups and similar to previously reported from other trials (Table 1). Greater than 70% of subjects completed study treatment in the lurasidone 80 mg (71.2%) and 160 mg groups (76.9%), and the QXR-600 mg group (80.8%), while a lower proportion of subjects in the placebo group completed treatment (60.7%; Fig. 1).

Table 1
Baseline characteristics of subjects randomized to treatment with lurasidone, quetiapine XR or placebo – safety population.

Characteristic	Treatment group							
	Lurasidone 80 mg/d (N=125)		Lurasidone 160 mg/d (N=121)		Quetiapine XR 600 mg/d (N=119)		Placebo (N=121)	
	n	%	N	%	n	%	n	%
Male	96	77	82	68	77	65	77	64
Race								
White	75	60	63	52	69	58	68	56
Black	22	18	29	24	19	16	25	21
Asian	24	19	25	21	26	22	24	20
Other	4	3	4	3	5	4	4	3
Ethnicity, Hispanic/Latino	10	8	8	7	10	8	10	8
Prior hospitalizations: ≥4	64	51	63	52	55	46	58	48
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, years	36.2	10.9	37.9	11.3	37.4	10.4	37.4	10.8
Age at onset of illness, years	24.6	8.3	25.7	7.8	24.5	8.6	25.5	8.6
Duration of illness, years	11.1	9.2	11.8	8.8	12.4	10.4	11.3	9.3
Duration of current episode, days	31.3	12.9	31.7	12.7	31.5	13.6	32.6	14.3
PANSS total score [a]	97.7	9.7	97.5	11.8	97.7	10.2	96.6	10.2
CGI-severity [a]	5.0	0.5	5.0	0.6	4.9	0.6	4.9	0.5
MADRS total score [a]	11.6	7.6	11.2	7.8	12.3	8.1	11.3	6.7

[a] Data for these parameters are based on the intent-to-treat population.

3.1. Efficacy

Using a mixed-model repeated-measures analysis, LS mean change (SE) from Baseline to Week 6 in PANSS total score was found to be significantly greater for the lurasidone 80 mg (−22.2 [1.8]; adjusted $p<0.001$) and 160 mg (−26.5 [1.8]; adjusted $p<0.001$) groups compared with the placebo group (−10.3 [1.8]) (Table 2). The LS mean change (SE) from Baseline to Week 6 in PANSS total score was also significantly greater for the QXR-600 mg group vs. placebo (−27.8 [1.8], $p<0.001$), thus confirming the assay sensitivity of the study. LS mean change from Baseline in the PANSS total score was similar for lurasidone 160 mg vs. QXR-600 mg (−26.5 vs. −27.8; unadjusted $p=0.62$; Bonferroni corrected $p=1.00$), however, this change was greater with QXR-600 mg compared with lurasidone 80 mg (−27.8 vs. −22.2; unadjusted for multiple comparisons, $p=0.028$; Bonferroni corrected, $p=0.056$).

Statistically significant separation from placebo (−2.4 [0.5]) on the PANSS total score was observed by Day 4 in the lurasidone 80 mg (−4.1 [0.5]; $p=0.014$) and 160 mg (−4.8 [0.5]; $p<0.001$) groups, and in the QXR-600 mg group (−4.0 [0.5]; $p=0.028$). Significant separation from placebo was also observed at each subsequent assessment week for each of the three study treatments (Fig. 2).

For the key secondary efficacy measure, the CGI-S, the LS mean change score from Baseline to Week 6 was significantly greater for both lurasidone treatment groups, and for QXR-600 mg, compared with the placebo group (Table 2).

A pairwise comparison of improvement at Week 6 (using MMRM) found trend level differences in favor of the 160 mg dose compared

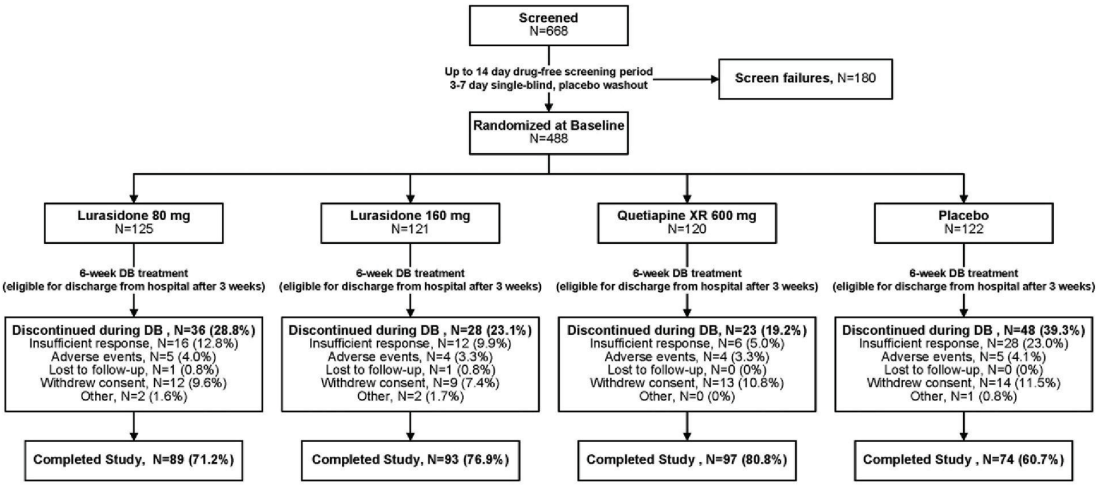

Fig. 1. Flow diagram and subject disposition.

Table 2
Change from baseline to week 6 on efficacy measures for patients with schizophrenia in a randomized, double-blind, placebo- and quetiapine XR-controlled study of lurasidone – intent-to-treat population.

Measure [a]	Treatment group							
	Lurasidone 80 mg/d (N=125)		Lurasidone 160 mg/d (N=121)		Quetiapine XR 600 mg/d (N=116)		Placebo (N=120)	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
PANSS[b]								
Total score change	−22.2***	1.8	−26.5***	1.8	−27.8***	1.8	−10.3	1.8
Positive subscale score change	−7.7***	0.6	−9.2***	0.6	−9.7***	0.6	−3.9	0.6
Negative subscale score change	−5.1***	0.4	−5.5***	0.4	−5.4***	0.4	−2.2	0.5
General psychopathology subscale score change	−10.0***	0.8	−12.3***	0.8	−12.9***	0.8	−5.0	0.9
CGI-Severity score change [b]	−1.5***	0.1	−1.7***	0.1	−1.7***	0.1	−0.9	0.1
NSA-16 total score change [c]	−7.8***	0.8	−8.9***	0.8	−8.6***	0.8	−3.4	0.8
MADRS total score change [c]	−4.0***	0.5	−4.4***	0.5	−4.3***	0.5	−1.0	0.5
Quality of well-being (SA) [c]	+0.67*	0.02	+0.71***	0.02	+0.71***	0.02	+0.63	0.02
Medication satisfaction questionnaire [c]	+1.5***	0.1	+1.6***	0.2	+1.8***	0.2	+0.7	0.2

*P<0.05; **P<0.01; ***P<0.001.
[a] Endpoint change scores are shown for all measures except the QWB-SA. PANSS: positive and negative symptom scale; CGI: clinical global impression scale; MADRS: Montgomery-Äsberg Depression Rating Scale; NSA-16: Negative Symptom Assessment Scale.
[b] p-values, comparing drug to placebo, are based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for pooled center, visit as a categorical variable, Baseline score, treatment and treatment by visit interaction, assuming an unstructured covariance matrix.
[c] p-values are based on an ANCOVA at Week 6 LOCF endpoint with treatment and pooled center as fixed factors and Baseline value as a covariate.

with the 80 mg dose of lurasidone on the PANSS total score (p=0.085) and the CGI-S score (p=0.057). For LOCF-endpoint change in the PANSS total score, the Cohen's d effect size was 0.58 for lurasidone 80 mg compared to 0.83 for lurasidone 160 mg; and for the CGI-S score, the Cohen's d effect size was 0.54 for lurasidone 80 mg compared to 0.81 for lurasidone 160 mg. The ANCOVA subgroup analyses showed no significant treatment interactions by gender, race, ethnicity, region, or age for either the PANSS total score or the CGI-S score.

Treatment with both doses of lurasidone and QXR-600 mg were associated with significantly greater Week 6 improvement, compared with placebo, in the PANSS positive and negative subscores (Table 2). Week 6 improvement in the NSA-16 scale was also significant for both doses of lurasidone and for QXR-600 mg (Table 2) compared with placebo.

The proportion of responders (≥20% improvement in PANSS total score from Baseline to LOCF-endpoint) was higher in subjects treated with lurasidone 80 mg (65%; p<0.001) and lurasidone 160 mg (79%; p<0.001) compared with subjects treated with placebo (41%). The proportion of responders was also higher for QXR-600 mg (79% vs. placebo, 41%; p<0.001). The responder rate was significantly higher for the 160 mg dose of lurasidone compared with the 80 mg dose (p=0.018), with an NNT of 8 (95%-CI, 5, 39).

Treatment with both doses of lurasidone and QXR-600 mg were associated with significantly greater Week 6 improvement in depressive symptoms assessed using the MADRS compared with the placebo group (Table 2); and significantly greater improvement in both the quality of well-being self-assessment (QWB-SA) scale, and the medication satisfaction questionnaire compared with the placebo group (MSQ; Table 2).

3.2. Safety

3.2.1. Body weight, body mass index (BMI), and waist circumference

Treatment with lurasidone 80 mg was associated with a small but significant increase in weight and BMI when compared with placebo, while changes in weight, BMI, and waist circumference were similar for the lurasidone 160 mg and placebo groups (Table 3). Clinically significant (≥7%) increase in weight was reported by a

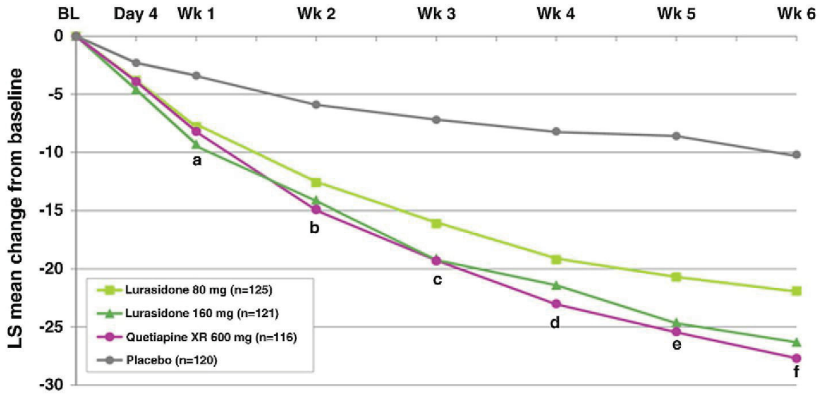

Fig. 2. Change from baseline in PANSS total score – mixed model repeated measurements analysis (MMRM. Intent-to-treat population). LS means and p-values were computed based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for pooled center, visit as a categorical variable, baseline score, treatment and treatment by visit interaction, assuming an unstructured covariance matrix. Comparisons with placebo: [a] Day 4: p=0.014 for lurasidone 80 mg; p<0.001 for lurasidone 160 mg; p=0.028 for quetiapine XR. [b] Week 1: p<0.001 for lurasidone 80 mg and 160 mg, and for quetiapine XR. [c] Week 2: p<0.001 for lurasidone 80 mg and 160 mg, and for quetiapine XR. [d] Week 3: p<0.001 for lurasidone 80 mg and 160 mg, and for quetiapine XR. [e] Week 4: p<0.001 for lurasidone 80 mg and 160 mg, and for quetiapine XR. [f] Week 5: p<0.001 for lurasidone 80 mg and 160 mg, and for quetiapine XR. [g] Week 6: p<0.001 for lurasidone 80 mg and 160 mg, and for quetiapine XR.

Table 3
Effect of 6 weeks of treatment with lurasidone, quetiapine XR, or placebo on weight, body mass index, waist circumference, and laboratory test results (week 6 LOCF-endpoint analysis, safety population).[a]

Measure	Treatment group							
	Lurasidone 80 mg/d		Lurasidone 160 mg/d		Quetiapine XR 600 mg/d		Placebo	
	n	Value	n	Value	n	Value	n	Value
Weight, kg, mean (SD)								
Baseline	125	76.1 (17.3)	121	74.4 (17.2)	119	72.1 (17.0)	121	75.85 (16.3)
Change	116	+0.6 (2.6)*	113	+0.6 (3.1)	111	+2.1 (3.3)***	115	+0.1 (2.5)
≥7% increase in weight, n (%)								
Week 6	116	5 (4.3)	113	5 (4.4)	111	17 (15.3)	115	3 (2.6)
Body mass index, kg/m^2, mean (SD)								
Baseline	125	25.7 (4.95)	121	25.6 (4.85)	119	25.5 (5.2)	121	26.1 (4.8)
Change	116	+0.2 (0.85)*	113	+0.2 (1.0)	111	+0.7 (1.1)***	115	+0.0 (0.8)
Waist circumference, cm, mean (SD)								
Baseline	125	88.3 (13.2)	121	87.0 (14.25)	119	87.35 (14.5)	121	88.4 (13.0)
Change	115	+0.9 (3.0)	110	+1.3 (3.8)	111	+1.8 (5.2)	115	+0.2 (3.0)
Total cholesterol, mg/dL, median								
Baseline	125	180.0	121	188.0	119	186.0	121	184.0
Change	111	−4.0	114	−7.5	107	+6.0***	111	−7.0
LDL cholesterol, mg/dL, median								
Baseline	125	107.0	121	112.0	119	111.0	121	111.0
Change	111	−3.0	114	−4.0	107	+4.0**	111	−3.0
HDL cholesterol, mg/dL, median								
Baseline	125	43.0	121	43.0	119	42.0	121	42.0
Change	111	0.0*	114	0.0	107	0.0*	111	−3.0
Triglycerides (mg/dL)								
Baseline	125	106.0	121	110.0	119	115.0	121	102.0
Change	111	−2.0	114	−9.0	106	+8.0*	111	−9.0
Glucose, mg/dL, median								
Baseline	125	92.0	121	90.0	119	91.0	121	93.0
Change	111	−1.0	112	0.0	107	+3.0	110	0.0
HbA1c, mean % (SD)								
Baseline	125	5.4 (0.4)	121	5.5 (0.45)	119	5.5 (0.5)	121	5.5 (0.4)
Change	109	+0.1 (0.4)	111	0.01 (0.28)	104	0.03 (0.31)	108	0.01 (0.30)
Insulin, mU/L, median								
Baseline	120	8.8	121	9.0	116	8.7	118	9.0
Change	106	−0.4	114	+0.5	104	+0.4	109	−0.3
Prolactin, ng/mL, median								
Baseline	125	7.5	121	8.6	119	8.7	121	10.1
Change	111	+0.8	114	+3.0***	107	−0.3	111	−0.8

* $p<0.05$; ** $p<0.01$; *** $p<0.001$.
Comparisons of the lurasidone and quetiapine XR groups vs. placebo at LOCF Endpoint are based on a rank ANCOVA analysis. Significance testing was not performed for waist circumference, HbA1c, and insulin.
[a] HbA1c = glycated hemoglobin; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

similar proportion of subjects in both the lurasidone 80 mg (n = 5; 4%) and 160 mg (n = 5; 4%) groups, and the placebo group (n = 3; 3%). In contrast, there was a significant mean increase in the QXR-600 mg group compared with the placebo group in both weight and BMI (Table 3), with 17 subjects (15%) having a clinically significant weight gain.

3.2.2. Metabolic parameters

Changes in lipid levels were comparable for both lurasidone dosage groups and the placebo group, while the QXR-600 mg group showed a significant median increase compared with the placebo group in levels of cholesterol, LDL, and triglycerides ($p<0.05$, LOCF-endpoint; Table 3). Changes in glucose and insulin were also comparable for both lurasidone groups, and the QXR-600 mg and placebo groups (Table 3). There were no clinically relevant changes in HbA1c values for any treatment group, and no endpoint differences for the lurasidone and QXR-600 mg treatment groups compared with placebo.

Categorical shifts from normal to high (abnormal) values for lipid and glucose parameters were as follows: total cholesterol (lurasidone 80 mg, 7.2%; lurasidone 160 mg, 5.3%; QXR-600 mg, 15.9%; placebo, 6.3%), LDL cholesterol (lurasidone 80 mg, 7.2%; lurasidone 160 mg, 6.1%; QXR-600 mg, 15.0%; placebo, 4.5%), triglycerides (lurasidone 80 mg, 2.7%; lurasidone 160 mg, 5.3%; QXR-600 mg 10.4%; placebo, 6.3%), glucose (lurasidone 80 mg, 15.3%; lurasidone 160 mg, 18.8%; QXR-600 mg, 26.2%; placebo 18.2%; Supplementary Table 1).

3.2.3. Prolactin and other laboratory values

Median changes in prolactin levels at Week 6 (LOCF) were comparable for the lurasidone 80 mg, QXR-600 mg and placebo groups, but were significantly higher for the lurasidone 160 mg group compared with placebo (Table 3). Additional gender-specific information on the effect of study treatment on prolactin is summarized in Supplementary Table 1. No other clinically relevant differences were noted for any other laboratory values when comparing either lurasidone treatment group to the placebo group.

3.2.4. Physical examination and vital signs

Orthostatic hypotension (systolic) occurred in 3 of 246 subjects (1.2%) in the combined lurasidone treatment groups, and in 4 of 17 subjects (3.4%) in the QXR-600 mg group; orthostatic tachycardia occurred in 7 of 246 subjects (2.8%) in the combined lurasidone treatment groups, and in 11 of 117 subjects (9.4%) in the QXR-600 mg group. There were no other clinically significant treatment-emergent changes in either of the lurasidone groups, or the QXR-600 mg group, compared with the placebo group, in physical examination findings or vital signs.

3.2.5. ECG

Treatment with lurasidone was not associated with any treatment-emergent ECG abnormalities compared with placebo. The mean LOCF-endpoint increase in the Bazett-corrected QT interval (QTcB) and

the Fridericia-corrected QT interval (QTcF), was 1.9 ms and 3.1 ms, respectively, in the lurasidone 80 mg group, 3.9 ms and 2.8 ms in the lurasidone 160 mg group, 10.4 ms and 3.0 ms in the quetiapine XR group, and 7.6 ms and 6.1 ms in the placebo group. There was no difference between the lurasidone 80 mg and 160 mg groups and the placebo group in the proportion of subjects with an increase from Baseline of ≥30 ms or ≥60 ms in QTc interval, either QTcB or QTcF. No subject in any treatment group had a QTc interval >500 ms.

3.2.6. Extrapyramidal symptoms and akathisia

The incidence of extrapyramidal-related adverse events was 11.2% in the lurasidone 80 mg group, 13.2% in the lurasidone 160 mg group, 5.9% in the QXR-600 mg group, and 0.8% in the placebo group (Supplementary Table 2). Parkinsonism was the most frequently reported EPS-related event, reported by 5.6% of subjects in the lurasidone 80 mg group, 6.6% of subjects in the lurasidone 160 mg group, 3.4% of subjects in the QXR-600 mg group, and no subjects in the placebo group. The incidence of akathisia was 8.0% in the lurasidone 80 mg group, 7.4% in the lurasidone 160 mg group, 1.7% in the QXR-600 mg group, and 0.8% in the placebo group (Table 4). The effect of study treatment on movement disorder signs or symptoms, as measured by change in SAS, BAS, and AIMS scores, was generally absent to mild in subjects treated with lurasidone. There were relatively small LS mean (±SE) changes at Week 6 (LOCF) in the BAS total score and SAS mean scores, respectively, in subjects treated with lurasidone 80 mg (−0.1±0.1; −0.01±0.01) and 160 mg (+0.1±0.1; 0.00±0.01), QXR-600 mg (−0.2±0.1; −0.05±0.01), and placebo (−0.1±0.1; −0.03±0.01). Fewer than 5% of lurasidone-treated subjects showed a categorical shift at Week 6 (LOCF) from absent/mild to moderate-to-severe symptoms in any BAS item. There were minimal-to-no changes from Baseline in the AIMS total score for any treatment group.

The proportion of subjects receiving an as-needed anticholinergic medication was 16% in the lurasidone 80 mg group, 17% in the lurasidone 160 mg group, 9% in the QXR-600 mg group, and 0.8% in the placebo group.

Discontinuations due to extrapyramidal adverse events occurred in 0.8% of subjects in the lurasidone 80 mg group, 0.8% in the lurasidone 160 mg group, 0.8% in the QXR-600 mg group, and no subjects in the placebo group. Discontinuations due to akathisia occurred in 1.6% of subjects in the lurasidone 80 mg group, 0.8% in the lurasidone 160 mg group, and in no subjects in the QXR-600 mg and placebo groups.

3.2.7. Epworth Sleepiness Scale (ESS)

At Baseline, the LS mean (±SE) ESS total scores were similar for the lurasidone 80 mg (6.1±0.4) and 160 mg (6.3±0.4) groups, the QXR-600 mg group (6.1±0.4), and the placebo group (6.4±0.4), indicating a slight chance of dozing or sleeping during daytime hours. At Week 6 (LOCF), treatment with lurasidone 80 mg and 160 mg, respectively was associated with a similar decrease (i.e., improvement) in LS mean (±SE) ESS total scores compared to placebo (−1.1±0.3 and −0.7±0.3 vs. −0.9±0.3; $p>0.50$ for both comparisons). In contrast, treatment with QXR-600 mg was associated with a significant increase in the ESS total score compared with both placebo (+0.6±0.3 vs. −0.9±0.3; $p=0.001$), and with lurasidone 80 mg ($p<0.001$) and 160 mg ($p<0.001$).

3.2.8. Adverse events

A comparable proportion of subjects in the lurasidone, QXR-600 mg, and placebo groups experienced at least one adverse event (Table 4). The majority of adverse events in all treatment groups were rated as mild to moderate. A similarly low proportion of subjects reported at least one adverse event reported as "severe" on lurasidone 80 mg (n=4; 3.2%), lurasidone 160 mg (n=4; 3.3%), QXR-600 mg (n=3; 2.5%) and placebo (n=7; 5.8%). Rates of discontinuations due to adverse events were relatively low in the lurasidone 80 mg group (4.0%), the lurasidone 160 mg group (3.3%), and the QXR-600 mg group (3.3%) and were comparable to those in the placebo group (4.1%). Adverse events that occurred with an incidence of at least 5% are summarized in Table 4. No clear dose–response effect on the incidence of adverse events was observed for lurasidone. There were no treatment-emergent deaths during the study. Serious adverse events are summarized in Supplementary Table 3.

4. Discussion

The results of this double-blind, placebo-controlled, multiregional trial indicate that lurasidone, at fixed dosages of 80 and 160 mg/d, was an effective and well-tolerated treatment for subjects experiencing an acute exacerbation of chronic schizophrenia. These findings have led to approval of the lurasidone in the dosing range of 40–160 mg/d for the treatment of schizophrenia in the US and elsewhere (Latuda USPI, 2012).

Treatment with lurasidone 160 mg/d was associated with a trend to greater improvement on both the PANSS total and CGI-S scores when compared with the 80 mg dose, which is reflected in the Cohen's d effect size findings (0.83 vs. 0.58 for lurasidone 160 mg/d

Table 4
Incidence of adverse events reported in ≥5% of subjects during 6 weeks of treatment with lurasidone, quetiapine XR, or placebo (safety population).

	Lurasidone 80 mg/d (N=125)		Lurasidone 160 mg/d (N=121)		Quetiapine XR 600 mg/d (N=119)		Placebo (N=121)	
	n	%	n	%	n	%	n	%
At least one adverse event	72	57.6	76	62.8	71	59.7	75	62.0
Headache	12	9.6	12	9.9	13	10.9	13	10.7
Insomnia	14	11.2	8	6.6	5	4.2	11	9.1
Akathisia	10	8.0	9	7.4	2	1.7	1	0.8
Nausea	10	8.0	8	6.6	4	3.4	4	3.3
Vomiting	8	6.4	9	7.4	6	5.0	6	5.0
Anxiety	9	7.2	4	3.3	1	0.8	10	8.3
Dizziness	6	4.8	7	5.8	16	13.4	2	1.7
Somnolence	5	4.0	8	6.6	16	13.4	1	0.8
Agitation	4	3.2	6	5.0	3	2.5	10	8.3
Dyspepsia	3	2.4	7	5.8	3	2.5	4	3.3
Constipation	3	2.4	1	0.8	8	6.7	3	2.5
Dry mouth	2	1.6	2	1.7	9	7.6	1	0.8
Arthralgia	2	1.6	1	0.8	7	5.9	1	0.8
Upper respiratory tract infection	2	1.6	1	0.8	6	5.0	1	0.8
Weight increased	1	0.8	2	1.7	8	6.7	1	0.8
Psychotic disorder	0	0	0	0	3	2.5	7	5.8

vs. 80 mg/d). In addition, lurasidone 160 mg/d was associated with a significantly higher endpoint responder rate compared to 80 mg/d (79% vs. 65%, $p<0.001$). These findings contribute to a more complete understanding of lurasidone dose–response in patients with schizophrenia and provide an evidence base for use of higher lurasidone doses where this is judged to be clinically appropriate.

The efficacy advantage of the 160 mg dose of lurasidone was not accompanied by a dose-related increase in the incidence or severity of most adverse events compared with lurasidone 80 mg. In addition, there were no between-dose differences in the discontinuation rate due to adverse events (<5% in both lurasidone dosage groups), or in the incidence of individual adverse events, or events rated as "severe". There were no clinically meaningful differences between the 80 mg or 160 mg doses of lurasidone and placebo in effects on weight, total cholesterol, LDL, triglycerides, insulin, glucose, or HbA1c. The lack of a dose-relationship for weight and metabolic effects in the current study is consistent with results from previous fixed-dose, placebo-controlled trials of lurasidone in the range of 40–120 mg/d (Nakamura et al., 2009; Meltzer et al., 2011), and extends these prior findings to the 160 mg/d dose. The minimal effect of lurasidone on weight is consistent with pharmacology studies indicating that lurasidone has no clinically relevant affinity for receptors hypothesized to be associated with weight gain: H_1-histamine (Ki, >1000) or 5-HT_{2C} (Ki, 415; Kroeze et al., 2003; Ishibashi et al., 2010; Correll et al., 2011). The apparent absence of a dose-related effect of lurasidone on weight and metabolic parameters differs from dose-dependent effects reported for some other atypical antipsychotics (clozapine, olanzapine, and possibly quetiapine; Simon et al., 2009; de Hert et al., 2011). Treatment with lurasidone 160 mg/d, compared with the 80 mg/d dose, was not associated with an increase in discontinuations due to adverse events, or in the severity of adverse events. Although akathisia frequency did not increase, a small increase in frequency of EPS-related adverse events was observed at the higher lurasidone dose. In addition, some increase in the frequency of somnolence and dyspepsia was observed at the higher lurasidone dose. We note that this was the first lurasidone placebo-controlled trial involving patients with schizophrenia where study medication was administered (with food) in the evening. This dosing strategy may in part account for the lower rate of adverse events, including akathisia, compared to prior studies.

The low propensity of lurasidone for adverse effects on weight and metabolic outcomes throughout its therapeutic dose range is an important safety finding since schizophrenia, and its treatment, is associated with a high degree of cardiometabolic risk that contributes substantially to the excess mortality observed with the illness (Osby et al., 2000; Goff et al., 2005; Saha et al., 2007). In a recent meta-analysis, approximately one-third of patients diagnosed with schizophrenia met criteria for metabolic syndrome (Mitchell et al., 2012). Rates have been reported to be even higher in some patient populations such as the CATIE schizophrenia study (41%; McEvoy et al., 2005), in patients with longer illness durations, and in patients who have been treated with atypical antipsychotics with established adverse effects on weight and metabolic parameters, such as clozapine and olanzapine (de Hert et al., 2011; Mitchell et al., 2012).

In this 6 week study, lurasidone was associated with a dose-related increase in prolactin levels, primarily in female subjects, with the 80 mg/d dose showing an effect that was comparable with placebo, while treatment with the 160 mg/d dose resulted in a greater median increase compared with placebo (+3.0 vs. −0.8 ng/mL; LOCF). Change in prolactin in the QXR-600 mg treatment group was comparable to that of placebo.

Treatment with QXR-600 mg was associated with significant endpoint improvement vs. placebo in the PANSS total score, CGI-S score, and other secondary measures. The magnitude of improvement observed for QXR-600 mg in the current study was comparable or greater than that reported in previous placebo-controlled short-term trials with both the IR and XR formulations (Kahn et al., 2007; Lindenmayer et al., 2008; Baldwin and Scott, 2009). There was no difference between QXR-600 mg and the 160 mg dose of lurasidone in change from Baseline on the PANSS total score. Improvement in the PANSS total score was significantly greater for QXR-600 mg compared with lurasidone 80 mg, however this finding was of borderline significance after Bonferroni correction for multiplicity.

The frequency of adverse events in the QXR-600 mg group in the current study was also consistent with results reported from previous studies (Meulien et al., 2010). The most frequent adverse events reported for QXR-600 mg were somnolence, orthostatic dizziness, headache, weight gain, and anticholinergic-related events such as dry mouth and constipation. Treatment with QXR-600 mg was associated with a higher proportion of subjects with clinically meaningful weight gain, and a higher proportion of subjects with clinically meaningful increases in levels of total cholesterol, LDL, triglycerides, and glucose than with lurasidone treatment. The effect of QXR-600 mg on weight and metabolic parameters observed in the current study are consistent with previous reports (Meulien et al., 2010; Rummel-Kluge et al., 2010). In the present study, the incidence of orthostatic hypotension (3.4%) and tachycardia (9.4%) were somewhat lower than rates reported in previous short-term trials with QXR (Meulien et al., 2010).

Because somnolence is a significant risk factor for nonadherence and impairment in cognitive function and quality of life, a validated measure, the Epworth Sleepiness Scale, was utilized to systematically evaluate this adverse effect in the current study (Johns, 1991; Velligan et al., 2006; Kane and Sharif, 2008; Dibonaventura et al., 2012). Treatment with both the 80 mg/d and 160 mg/d doses of lurasidone were associated with endpoint reduction in the Epworth Sleepiness Scale total score (improvement in somnolence), while treatment with QXR-600 mg was associated with a significant increase in daytime somnolence compared with both doses of lurasidone, and with placebo. The affinity of selected atypical antipsychotics for the H_1 receptor (e.g., clozapine, olanzapine, quetiapine, risperidone), appears to be correlated with risk of somnolence. In contrast, lurasidone has been reported to lack affinity for the H_1 receptor (Ishibashi et al., 2010). In the current trial, study medication was taken in the evening, which may have limited the incidence of daytime somnolence for both drugs.

Several potential study limitations should be noted. First, use of a fixed-dose design facilitated assessment of dose–response effects, but may have reduced the ability of the investigator to optimize the tolerability of study drug. Despite this potential limitation, both lurasidone and QXR-600 mg were well-tolerated, with a low incidence of adverse events, and a low attrition rate. Second, in order to optimally evaluate treatment effect, study entry criteria required patients to be experiencing an acute exacerbation of psychosis, while limiting medical comorbidity and use of concomitant medications. This may have reduced the generalizability of the study results.

In summary, the results of the current study demonstrated that lurasidone 80 mg and 160 mg, administered once daily in the evening with food, were efficacious treatments for subjects with an acute exacerbation of chronic schizophrenia. Study findings suggest that lurasidone 160 mg may be associated with some efficacy advantages over the 80 mg dose. There were no dose-related effects for lurasidone on weight, metabolic parameters, akathisia or other movement disorders, or QTc interval. Differences in the benefit-risk profile of lurasidone and QXR-600 mg during the current short-term trial were primarily safety related. Treatment with QXR-600 mg was associated with significant short-term effects on weight, other metabolic parameters and daytime somnolence compared with lurasidone, and less effect on prolactin. The current results suggest that the lurasidone 160 mg dose may be appropriate for patients with schizophrenia who require additional efficacy benefit beyond that obtained at lower doses, but may be associated with a slightly higher incidence of selected adverse events in some patients, including an increase in prolactin, somnolence and Parkinsonism but not akathisia.

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Contributors

Drs. Loebel, Cucchiaro, Sarma, Xu, Hsu, Kalali, Pikalov, and Potkin 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

Dr. Potkin has received grant funding from Astra-Zeneca, Bioline, Bristol-Myers Squibb, Sunovion, Elan, Forest Laboratories, Fujisawa Healthcare, Janssen Pharmaceutica, Merck, Novartis, Ono, Organon, Otsuka, Pfizer Inc., Solvay Pharmaceuticals, Roche, NIH, Harvard-Massachusetts General Hospital, Brigham and Women's Hospital, Vanda Pharmaceuticals Inc., and Wyeth. He also serves as an investigator for Vanda Pharmaceuticals Inc., and as a consultant/advisory board member for the American Psychiatric Association, AstraZeneca, Bioline, Bristol-Myers Squibb, Cortex, Sunovion, Janssen Pharmaceutica, Merck, Novartis, Organon, Otsuka, Pfizer Inc., Roche, Schering Plough, and Vanda Pharmaceuticals Inc. He serves on the Speakers' Bureau for AstraZeneca, Bristol-Myers Squibb, International Society for CNS Clinical Trials and Methodology, Merck, Novartis, and Pfizer Inc.

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Appendix A. Supplementary data

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