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LURASIDONE VS. QUETIAPINE XR FOR RELAPSE PREVENTION IN SCHIZOPHRENIA: A 12-MONTH, DOUBLE-BLIND STUDY

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ABSTRACT

Objectives: To evaluate the efficacy and safety of lurasidone vs. quetiapine XR (QXR) in preventing relapse in subjects with chronic schizophrenia.

Methods: After completing an initial double-blind, placebo-controlled, 6 week trial with fixed doses of lurasidone (80 mg; 160 mg) or QXR (600 mg), subjects received 12 months of double-blind, flexible once-daily doses of lurasidone (40-160 mg) vs. QXR (200-800 mg). The primary a priori efficacy comparison was between subjects treated with lurasidone (n=139) and QXR (n=79) who were clinical responders after acute treatment. The primary endpoint, time-to-relapse, was analyzed using a Cox proportional hazards model, with a pre-specified non-inferiority margin for the risk of relapse hazard ratio of 1.93.

Results: Lurasidone was non-inferior to QXR in risk for relapse over the 12 month treatment period (hazard ratio 0.728, 95% CI [0.410, 1.295]). The risk of relapse in lurasidone treated subjects was reduced by 27.2% (hazard ratio 0.728) compared with QXR. The Kaplan-Meier estimate of the probability of relapse at 12 months was lower for lurasidone vs. QXR (0.237 vs. 0.336). Treatment with lurasidone (modal daily dose 120 mg) was associated with a significantly greater change in PANSS total scores compared with QXR (modal dose 600 mg) on an MMRM analysis. Rates of adverse events ≥5% in the lurasidone group were akathisia (12.6%), headache (10.6%), insomnia (7.9%), anxiety (6.0%), parkinsonism (6.0%), and weight increased (6.0%). Analysis of changes from acute study baseline to 12 months of treatment (OC) with lurasidone and QXR, respectively, showed a mean change in weight of +0.7 vs. +1.2 kg; a median change in glucose of +1.0 vs. +1.0 mg/dL; a median change in cholesterol of 0.0 vs. +4.0 mg/dL; and a median change in triglycerides of -18.0 vs. -7.0 mg/dL. There were no clinically meaningful changes in other laboratory or ECG parameters on either drug.

Conclusions: This long-term, double-blind study demonstrated non-inferiority of lurasidone to QXR in prevention of relapse over a 12 month period, with a 27.2% reduction in relapse risk compared with QXR. Treatment with lurasidone was associated with a low rate of adverse effects on metabolic parameters and weight.

INTRODUCTION

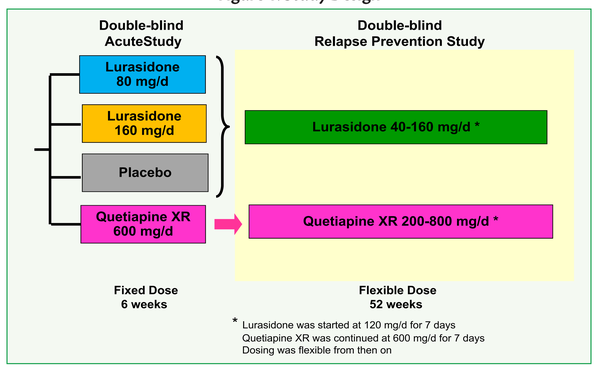
- Lurasidone has potent binding affinity for D_2, 5-HT_{2A} and 5HT_7 receptors (antagonist effect), moderate affinity for 5HT_{1A} (partial agonist effect) and a_{2C} receptors (antagonist effect), and no appreciable affinity for H_1 and M_1 receptors
- Lurasidone has demonstrated significant efficacy in the treatment of schizophrenia in a series of short-term, placebo-controlled trials (Nakamura et al, 2009; Potkin et al, 2011; Meltzer et al, 2011; Loebel et al, 2011)

OBJECTIVE

- The primary objective of this study was to utilize a non-inferiority design to evaluate the relapse prevention efficacy of lurasidone versus quetiapine XR in subjects with schizophrenia who had responded to 6 weeks of treatment for an acute exacerbation

METHODS

Figure 1. Study Design



Efficacy

- Primary: a non-inferiority analysis compared time-to-relapse for lurasidone vs. quetiapine XR utilizing a Cox proportional-hazards model (country as a covariate). The primary was between subjects treated with lurasidone (n=139) and quetiapine XR (n=79) who were clinical responders after acute treatment (subjects on placebo in the acute study were not included in this comparison)
- Lurasidone was to be declared as non-inferior to quetiapine XR in preventing relapse if the upper bound of a 2-sided 95% confidence limit for the hazard ratio of lurasidone vs. quetiapine XR was no greater than a non-inferiority margin of 1.93 corresponding to a maximum 15% difference in expected relapse rates based on an estimated 35% rate for lurasidone, and a 20% rate for quetiapine XR
- Relapse criteria prespecified per protocol:
  - ≥30% increase in PANSS from baseline of current study, and CGI-S ≥3
  - Re-hospitalization for worsening of psychosis
  - Emergence of suicidal ideation, homicidal ideation and/or risk of harm to self or others

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RESULTS

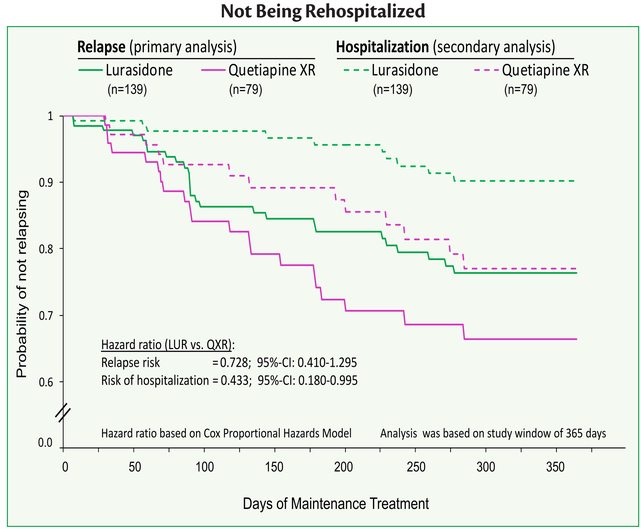
Table 1. Baseline Characteristics and Subject Disposition

	Lurasidone (N=151)		Quetiapine XR (N=85)	
	n	%	n	%
Male	108	72	52	61
White	87	58	56	66
	Mean		Mean	
Age, years	37.1		38.5	
Duration of illness, years	10.8		13.2	
PANSS Total score (DB baseline)*	97.7		97.9	
MADRS total score (DB baseline)*	12.0		12.8	
	n	%	n	%
Completed study	78	51.7	33	38.8
Discontinued prematurely	73	48.3	52	61.2
Insufficient response/clinical worsening	14	9.3	18	21.2
Adverse event	10	6.6	4	4.7
Withdrew consent	29	19.2	19	22.4
Lost to follow-up	10	6.6	9	10.6
Miscellaneous	10	6.6	2	2.4

* Based on n=132 for lurasidone, and n=72 for quetiapine XR

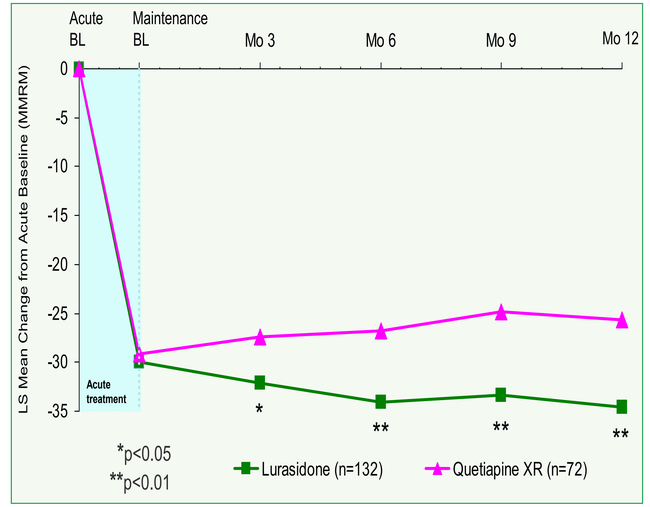
- Modal daily dose: LUR-40 mg (3%), LUR-80 mg (12%), LUR-120 mg (58%), LUR-160 mg (28%), The mean modal daily dose of lurasidone was 124.2 mg
- Modal daily dose: QXR-200 mg (1%), QXR-400 mg (11%), QXR-600 mg (56%), QXR-800 mg (32%), The mean modal daily dose of quetiapine XR was 637.6 mg

Figure 2. Kaplan-Meier Plots of the Probability of Not Relapsing and Not Being Rehospitalized



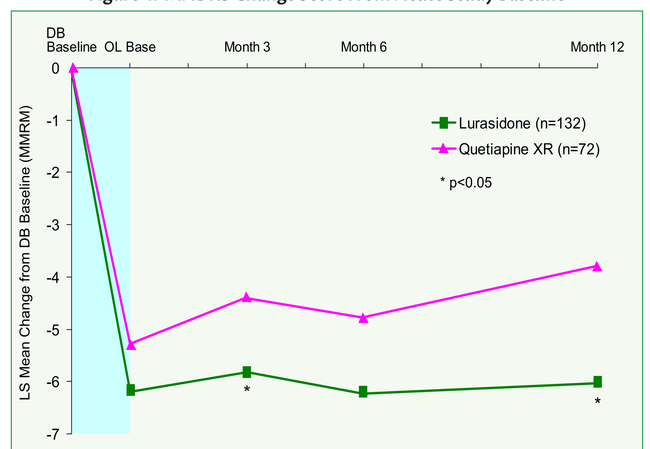
- The probability of relapse at 12 months was 23.7% for lurasidone and 33.6% for quetiapine XR
- For overall relapse risk, the upper limit of the hazard ratio (1.295) is lower than the pre-specified non-inferiority margin (1.93), therefore the non-inferiority of lurasidone vs. QXR was demonstrated in this study

Figure 3. PANSS Total Change Score From Acute Study Baseline



- Treatment with lurasidone was also significantly different from quetiapine XR in change from the DB baseline of the current study on the PANSS total score at Month 3 (-1.8 vs. +1.3; p<0.05), Month 6 (-3.8 vs. +1.8; p=0.002), Month 9 (-3.6 vs. +3.0; p=0.005), and Month 12 (-5.0 vs. +1.7; p=0.010)

Figure 4. MADRS Change Score From Acute Study Baseline



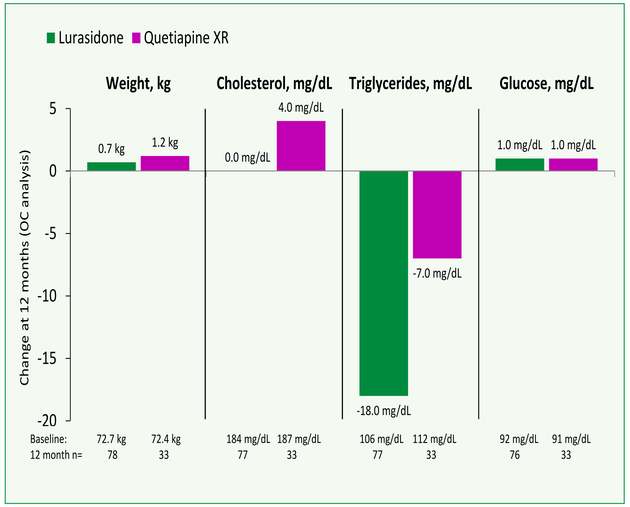
Based on a repeated measures linear regression model of the change from the DB acute baseline score, with fixed effects for pooled center, visit as a categorical variable, baseline score, treatment and treatment by visit interaction, assuming an unstructured covariance matrix

DISCLOSURE

A. Loebel, J. Cucchiaro, J. Xu, K. Sarma and A. Pikalov are all full-time employees of Sunovion Pharmaceuticals Inc. A. Kalali is a full-time employee of Quintiles which was working under contract with Sunovion in the conduct of this study.

Dr. Kane has been a consultant, or participated in advisory boards or speakers' bureaus, for Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cephalon, Inc., Dainippon Sumitomo, Eisai Inc., Eli Lilly, H. Lundbeck A/S, Intracellular Therapeutics, Janssen Pharmaceutica, Johnson and Johnson, Merck, Myriad, Novartis, Otsuka Pharmaceutical, Pfizer, Proteus Biomedical, Rules Based Medicine, Shire, Takeda, Targacept, Vanda Pharmaceuticals, Wyeth, and holds stock in MedAvante, Inc.

Figure 5. Mean Change in Weight and Median Change in Metabolic Parameters at 12 Months (OC Analysis)



- Median change in prolactin at 12 months was +0.6 ng/dL on lurasidone and -0.7 ng/dL on quetiapine XR

Table 3. Incidence of Adverse Events Reported in ≥ 5% of Subjects

	Lurasidone (n=151)		Quetiapine XR (n=85)	
	n	%	n	%
At least one adverse event	97	64.2	61	71.8
Akathisia	19	12.6	2	2.4
Headache	16	10.6	8	9.4
Insomnia	12	7.9	8	9.4
Anxiety	9	6.0	3	3.5
Parkinsonism	9	6.0	0	0
Weight increased	9	6.0	7	8.2
Schizophrenia	7	4.6	13	15.3
Agitation	6	4.0	5	5.9
Psychotic disorder	6	4.0	7	8.2

CONCLUSIONS

- In this study, lurasidone was non-inferior to quetiapine XR in time to relapse (based on a pre-specified non-inferiority margin of 1.93) in this 12 month double-blind study
- Based on a Cox proportional hazards model, 12 months of treatment with lurasidone was associated with a 27.2% reduction in risk of relapse versus to quetiapine XR
- The risk of rehospitalization over 12 months of treatment was significantly lower on lurasidone (7.2%) compared to quetiapine XR (16.5%)
- During 12 months of treatment, improvement in the PANSS total and MADRS scores were significantly greater for the lurasidone group versus the quetiapine XR group
- Treatment with lurasidone was associated with minimal effects on weight, lipids, glycemic control, and prolactin
- The most common adverse events for lurasidone were: akathisia, headache, insomnia, anxiety, parkinsonism and increased weight