

A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia

BACKGROUND:

- Schizophrenia is a chronic, debilitating mental illness which usually requires long-term treatment with antipsychotic agents to control symptoms and minimize risk of relapse.
- Lurasidone is an atypical antipsychotic approved for treatment of schizophrenia in the U.S. and European Union.

OBJECTIVE:

- To evaluate the efficacy of lurasidone as a maintenance treatment for patients with schizophrenia.

METHODS

- **Design:** Double-blind, placebo-controlled, randomized, parallel experimental, withdrawal study. Patients randomized to placebo or lurasidone in a 1:1 ratio.
- **Duration:** Conducted between October 2011 & August 2013 at 71 sites in the US, Slovakia, Russia, Serbia, France, South Africa, & Italy
- **Inclusion criteria:** patients aged 18-75 years old, diagnosed with schizophrenia (based on DSM-IV-TR criteria) and experiencing an acute exacerbation. Entry criteria included a Positive and Negative Syndrome Scale (PANSS) total score of ≥ 80 with a score ≥ 4 on one or more positive subscale items, and a Clinical Global Impressions-Severity (CGI-S) score of ≥ 4 .
- **Exclusion criteria:** diagnoses of another Axis I or II disorder which had been a primary focus of treatment during the previous 3 months, a history of treatment resistance to antipsychotic agents, or evidence of current or recent substance abuse or suicidal ideation.
- **Primary outcome measure:** Primary efficacy endpoint was time to relapse (based on Kaplan-Meier survival analysis).
- **Secondary outcome measures:**
 - Open label
 - Safety assessments, which included treatment-emergent adverse events, movement disorder signs or symptoms, suicidal ideation, laboratory measures, vital signs, and ECG
 - Double blind
 - Change from double-blind baseline in PANSS and CGI-S scores
 - Safety assessments, which were similar to those in the open-label phase
- **Number of patients in each group:** 948 patients were screened for the open label phase, 676 were treated. 285 were randomized to double blind phase, 144 lurasidone & 141 placebo
- **Power:** It was determined that 98 relapse events would be required to detect a difference with 90% power
- **Data handling method:** intent to treat method

RESULTS

- **Number that completed the study:** 144 patients in lurasidone group; 69 discontinued, 47 terminated at study completion. 141 patients in placebo group; 82 discontinued, 39 terminated at study completion
- **Primary outcome measure:** Lurasidone significantly delayed time to relapse compared with placebo (log-rank test, $p=0.039$) reflecting a 33.7% reduction in risk of relapse (Cox model hazard ratio (95% CI), 0.663 (0.447–0.983); $p=0.041$). At the week 28 endpoint of the double-blind phase, the Kaplan–Meier estimate for probability of relapse was 42.2% for patients receiving lurasidone compared with 51.2% for the placebo group, which represents a 9% absolute difference in risk between treatment & placebo groups. NNT was 12, meaning that 12 patients would need to be treated with lurasidone for 1 relapse to be prevented compared to treating with placebo.

- **Secondary outcome measures:** Fewer patients discontinued from the lurasidone group (47.9%) than from the placebo group (58.2%) during the double-blind phase. 29.9% of patients in the lurasidone group and 41.1% in the placebo group discontinued from the study due to an observed relapse event. Among patients who experienced a relapse, psychiatric hospitalization due to worsening schizophrenia was reported in 9.3% of lurasidone treated patients and 12.1% of patients receiving placebo. Patients receiving placebo had greater worsening in PANSS total and CGI-S scores over the double-blind phase compared to patients receiving lurasidone however, this was not statistically significant at the week 28 endpoint. 200 patients (70.2%) were randomly assigned at US sites and 85 patients (29.8%) at non-US sites. Compared with placebo, lurasidone significantly delayed time to relapse in the non-US subgroup but not the US subgroup. In the double-blind phase, the percentage of patients reporting any adverse event was similar between groups 53.5% of lurasidone patients and 54.6 % placebo patients. The most common adverse events were akathisia, insomnia, headache, nausea, and anxiety. Serious adverse events were more common in the placebo group (7.8%) compared with the lurasidone group (4.2%), with schizophrenia and psychotic disorder as the most common. 46.2% of patients had a history of previous suicidal ideation or behavior. During the study, suicidal ideation emerged in 6.3% of patients during the open-label phase and in 1.4% of patients randomized to lurasidone, compared with 3.5% of patients randomized to placebo in the double-blind phase; there were no suicide attempts. Change in movement disorder signs or symptoms were generally absent to mild in patients treated with lurasidone.

STRENGTHS

- Parallel, experimental study
- Large sample size
- Appropriate power
- Correct use of statistical tests

LIMITATIONS

- Significant source of bias from the Sunovion employed authors
- Concomitant use of other medications
- Use of a placebo instead of an active control
- Low dosing of lurasidone
- Discontinued lurasidone abruptly instead of tapering off
- Open-label period to decrease the rates of adverse effects shown by lurasidone
- Benefit of lurasidone diminished significantly as time progressed - longer study period would be more appropriate

CONCLUSIONS

- More research is needed to evaluate longer-duration of treatment with Lurasidone & chance of relapse rates when the medication is tapered off appropriately.

Reference: Tandon R, Cucchiari J, Phillips D, Hernandez D, Mao Y, Pikalov A, Loebel A. A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia. *J Psychopharmacol.* 2016 Jan;30(1):69-77.