Efficacy and Safety of Lumateperone for Treatment of Schizophrenia

BACKGROUND:

- Schizophrenia is a chronic burdensome disease that has no cure. The Global Burden of Disease study found schizophrenia to have the highest functional burden of 235 physical and mental health states.
- Current treatment options have unfavorable side effects, lumateperone's unique mechanism of action (5-HT2A antagonist, D2 presynaptic partial agonist and postsynaptic antagonist, D1-receptor dependent glutamate modulator, and serotonin receptor inhibitor) may have a better safety profile.

OBJECTIVE:

- Evaluate the efficacy and safety of lumateperone tosylate for short-term treatment of schizophrenia verses placebo.

METHODS

- **Design:** randomized, double-blind, placebo-controlled trial. Consisted of 2-7 day screening period, 4 week treatment period, follow-up 2 weeks after last dose of medication.
- **Inclusion criteria:** 18-60 years old, clinical diagnosis of schizophrenia diagnosed by DSM-5, confirmed by DSM-IV-TR Axis I disorders, experiencing acute exacerbation of psychosis total score >/=40 on the Brief Psychiatric Rating Scale, 7-point Liker scale score of 4 or higher on 2 or more positive symptoms, onset of acute episode within 4 week of screening, score of 4 or more on Clinical Global Impression-Severity Scale of Illness (CGI-S) at screening and baseline, PANSS score of 70 or more (mod-severe) previous response to antipsychotic therapy.
- **Exclusion criteria:** unable to provide informed consent; pregnant and/or breast-feeding; dementia, delirium, mental retardation, epilepsy, drug-induced psychosis, brain trauma; schizoaffective disorder, bipolar disorder, major depression with psychotic features; imminent danger to self or others; suicidal ideation or behavior; unstable living environment; use of depot antipsychotic within 1.5 treatment cycles before baseline; use of any antipsychotic within the screening period; use of specific agents with known interaction with 5-HT_{2A} receptors; clinically abnormal laboratory values or medically relevant clinical findings; uncontrolled angina, recent history of myocardial infarction, clinically significant cardiac arrhythmia; hematological, renal, hepatic, endocrinological, neurological, cardiovascular disease; history of neuroleptic malignant syndrome; HIV; hepatitis B or C with evidence of active liver disease; substance abuse or dependence; positive drug or alcohol screen; likely drug allergy/hypersensitivity; prior participation in a study with lumateperone or exposure to any investigational product within 3 months of Day −1; unable to be safely discontinued from current antipsychotic or other psychotropic medications; any patient judged by the investigator to be inappropriate for study participation.
- **Primary measures:** Mean change from baseline to day 28 on the Positive and Negative Syndrome Scale (PANSS) v. placebo.
- **Secondary measures:** mean change from baseline to day 28 in CGI-S score, PANSS positive, negative, and general psychopathology subscales, the Personal and Social Performance (PSP) scale, the PANSS-derived prosocial factor, and the Calgary Depression Scale for Schizophrenia.
- 90% power to detect a difference in change in PANSS score from baseline to day 28 between lumateperone and placebo. Power was calculated with a sample size of 150 participants per arm.
- Data handling was a modified intent to treat.

RESULTS

- 359 participants completed the entire study; 128 in the 42mg lumateperone group, 120 in the 28mg lumateperone, and 111 in the placebo group.
- **Primary outcome measures:** improvement from baseline to day 28 in PANSS total score was statistically significant for the 42mg lumateperone group (-15.6 (SE 1.21) least-squares mean difference [LSMD] −4.2; 95% CI, −7.8 to −0.6, multiplicity adjusted p= 0.04) than placebo (-12.4 (SE 1.15)), but improvement in the 28mg lumateperone (-13.7 (SE 1.22), [LSMD] -2.6; 95% CI, −6.2 to 1.1, adjusted p=0.18) was not significant.
- **Secondary outcome measures:** change in CGI-S central score from baseline to day 28 was statistically significant for both lumateperone 42mg group (-0.9 (SE 0.08), LSMD -0.3 95% CI -0.5 to -0.1, adjusted p=0.04) and 28mg lumateperone (-0.8 (SE 0.08) LSMD -0.2 95%CI -0.5 to 0, unadjusted p=0.03) compared to placebo (-0.6 (SE 0.08)). PANSS positive symptom subscale change from baseline to day 28 was significant for 42mg (-4.8 (SE 0.45), p= 0.006) compared to placebo (-3.1 (0.43)), but not 28mg (-4.4 (0.43)). PANSS negative symptom subscale change from baseline was not significant for either 42mg (-1.4 (0.41), p=0.09) or 28mg (-0.9 (0.39), p=.36) compared to placebo (-0.7 (SE0.45)).
- **Authors conclusions:** Lumaterperone's unique mechanism supports antipsychotic efficacy with a favorable safety profile compared to current treatment. This may give lumateperone a important place in therapy for schizophrenia patients.

STRENGTHS

- Used centralized raters to administer scales to reduce risk of bias
- Medication was administered by study personnel and a second person watched to make sure the patient took the medication.

LIMITATIONS

- All authors have affiliations with the study sponsor Intra-Cellular Therapies
- Strict inclusion/ exclusion criteria limit the population the results can be extrapolated onto.
- Short study duration did not allow for an evaluation of the long-term safety profile.

CONCLUSIONS

- Lumateperone 42mg (lumateperone tosylate 60mg) significantly improved PANSS scores and demonstrated a favorable safety profile, it may be a suitable option for patients who had unfavorable adverse effects
- While lumateperone may be a good treatment option due to its distinct mechanism and safety profile, the high cost (AWP unit price 52.80) may limit its usefulness in therapy.
- More studies are needed to get a full picture of lumateperone's place in schizophrenia treatmenomt, including studies comparing it against current treatment options. Longer duration studies should be conducted to evaluate lumateperone's long-term safety profile.

Reference: Correll CU, Davis RE, Weingart M, et al. Efficacy and Safety of Lumateperone for Treatment of Schizophrenia: A Randomized Clinical Trial [published online ahead of print, 2020 Jan 8] [published correction appears in JAMA Psychiatry. 2020 Feb 19;:]. *JAMA Psychiatry*. 2020;77(4):349-358. doi:10.1001/jamapsychiatry.2019.4379

Allegra Browne, PharmD Candidate
06.12.2020