same population to test its efficacy in not just Pacific Islanders, but all youth.
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Insulin Sensitivity and Glucose Metabolism of Olanzapine and Combination Olanzapine and Samidorphan: A Phase 1 Exploratory Study in Healthy Volunteers

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ABSTRACT: Background: A combination of olanzapine and samidorphan (OLZ/SAM) is in development for schizophrenia to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain. The objective of this phase 1 exploratory study was to assess metabolic treatment effects of OLZ/SAM.

METHODS: Healthy, non-obese adults (18–40 years) were randomized 2:2:1 to once-daily OLZ/SAM, olanzapine, or placebo for 21 days. Assessments included oral glucose tolerance test (OGTT), hyperinsulinemic-euglycemic clamp, weight gain, and adverse event (AE) monitoring. Treatment effects were estimated with analysis of covariance.

RESULTS: Sixty subjects were randomized (OLZ/SAM, n=24; olanzapine, n=24; placebo, n=12); 19 (79.2%), 22 (91.7%), and 11 (91.7%), respectively, completed the study. In the OGTT, olanzapine led to significant hyperinsulinemia (P<0.0001) and significantly reduced insulin sensitivity (2-hour Matsuda index) at day 19 vs baseline (P=0.0012), changes not observed with OLZ/SAM. No significant between-group differences were observed for change from baseline in clamp-derived insulin sensitivity index at day 21. Least squares mean weight change from baseline was similar with OLZ/SAM (3.16 kg) and olanzapine (2.87 kg); both were significantly higher than placebo (0.57 kg; both P<0.01). Caloric intake significantly decreased from baseline to day 22 with OLZ/SAM (P=0.015) but not with olanzapine or placebo. Forty-nine subjects (81.7%) experienced ≥1 AE (OLZ/SAM, 87.5%; olanzapine, 79.2%; placebo, 75.0%).

CONCLUSIONS: In this exploratory study, hyperinsulinemia and decreased insulin sensitivity were observed in the OGTT with olanzapine but not with OLZ/SAM or placebo. Clamp-derived insulin sensitivity index and weight changes were similar with OLZ/SAM and olanzapine in healthy subjects during the 3-week study.
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The Safety and Tolerability of Lumateperone 42 mg for the Treatment of Schizophrenia: A Pooled Analysis of 3 Randomized Placebo-Controlled Trials

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ABSTRACT: Introduction: Lumateperone (ITI-007) is in late-phase clinical development for schizophrenia. Lumateperone has a unique mechanism of action that modulates serotonin, dopamine, and glutamate neurotransmission.

This pooled analysis of lumateperone in 3 randomized, double-blind, placebo-controlled studies was conducted to evaluate the safety and tolerability of lumateperone 42mg (ITI-007 60mg).

METHODS: Data were pooled from the 3 controlled late-phase studies of lumateperone 42mg in patients with acute exacerbation of schizophrenia. Safety assessments of all patients who received at least one dose of any treatment included treatment-emergent adverse events (TEAEs), changes in laboratory parameters, extrapyramidal symptoms (EPS), and vital signs.

RESULTS: The safety population comprised 1,073 patients (placebo [n=412], lumateperone 42mg [n=406], risperidone [n=255]). TEAEs that occurred in the lumateperone 42mg group at a rate of ≥5% and twice placebo were somnolence/sedation (24.1% vs 10.0%) and dry mouth (5.9% vs 2.2%). Rates of discontinuation due to TEAEs with lumateperone 42mg (0.5%) were similar to placebo (0.5%) and lower than risperidone (4.7%). Mean change in weight and rates of EPS-related TEAEs were less for lumateperone 42mg and placebo patients than risperidone patients. Mean change from baseline in metabolic parameters were similar or smaller for lumateperone 42mg vs placebo. Mean changes were notably higher in risperidone patients vs lumateperone 42mg and placebo for glucose, cholesterol, triglycerides, and prolactin.

CONCLUSION: In this pooled analysis, lumateperone 42mg showed good tolerability with potential benefits over risperidone for metabolic, prolactin, and EPS risks. The only TEAE that occurred in >10% of lumateperone patients was somnolence/sedation, which was impacted by morning administration; in subsequent studies that administered lumateperone in the evening, somnolence/sedation rates were markedly reduced. These results suggest that lumateperone 42mg may be a promising new treatment for schizophrenia.

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Results From a 12-Month Open-label Safety Study of Lumateperone (ITI-007) in Patients with Stable Symptoms of Schizophrenia

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ABSTRACT: Introduction: Lumateperone (lumateperone tosylate, ITI-007) is an investigational drug for the treatment of schizophrenia, bipolar depression, and other disorders. Lumateperone has a unique mechanism of action that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission. This may provide advantages in the treatment of the broad symptoms associated with schizophrenia, including negative and depression symptoms. In 2 previous placebo-controlled trials in patients with acute schizophrenia, lumateperone 42mg (ITI-007 60mg) demonstrated statistically significant improvement in the Positive and Negative Syndrome Scale (PANSS) Total score compared with placebo. In these studies, lumateperone was well tolerated with a safety profile similar to placebo. This open-label long-term study evaluated the safety and effectiveness of lumateperone 42mg in patients with schizophrenia and stable symptoms.

METHODS: Patients with stable schizophrenia were treated for up to 1 year with lumateperone 42mg. Safety assessments included adverse events (AEs), body weight, laboratory parameters, and extrapyramidal symptoms (EPS)/motor symptom assessments. Efficacy analyses included evaluation of changes in PANSS Total score and in depression symptoms, as measured by the Calgary Depression Scale for Schizophrenia (CDSS).

RESULTS: In the 1-year open-label study, 602 patients received at least 1 dose of lumateperone 42mg; at the time of this interim analysis, 107 patients had completed 1 year of treatment. Only 4 TEAEs occurred in ≥5% of patients (weight decrease, dry mouth, headache and diarrhea); the majority of AEs were mild or moderate in intensity. Most metabolic parameters and mean prolactin levels decreased from SOC baseline, as did mean body weight and BMI. Based on AE reporting and EPS/motor symptom scales, lumateperone treatment was associated with minimal EPS risk. Lumateperone 42mg treatment was associated with significant reductions in PANSS Total score from baseline, with continuing PANSS improvement throughout the study. In patients with moderate-to-severe depression symptoms at baseline (CDSS>5), mean CDSS scores decreased from 7.4 (baseline) to 3.1 (Day 300); 60% of patients met CDSS response criteria (50% improvement from baseline) by Day 75 and this response rate was maintained through day 300. Similar magnitude of CDSS improvement was seen regardless of concurrent antidepressant therapy.

CONCLUSION: In long-term treatment, lumateperone was associated with minimal metabolic, EPS, and cardiovascular safety issues relative to current SOC antipsychotic therapy. Lumateperone improved schizophrenia symptoms with