Pharmacokinetic-Pharmacodynamic Analysis of Concentration-Response Relationship in Schizophrenia Patients Treated with Olanzapine or OLZ/SAM

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Abstract

Background. A combination of olanzapine and samidorphan (OLZ/SAM) that provides the efficacy of olanzapine while mitigating weight gain was recently approved by the Food and Drug Administration for the treatment of schizophrenia and bipolar I disorder. This exploratory population pharmacokinetic-pharmacodynamic analysis evaluated potential relationships between drug exposure and treatment effects.

Methods. Positive and Negative Syndrome Scale (PANSS) total score and/or bodyweight data from efficacy studies served as pharmacodynamic endpoints. Pharmacokinetic input came from predicted plasma drug concentrations using a population pharmacokinetic model for the corresponding studies. Regression and box plots were generated to investigate potential pharmacokinetic-pharmacodynamic relationships.

Results. PANSS total score and/or bodyweight records were paired with olanzapine and/or samidorphan concentrations from 1464 patients with schizophrenia. Within the clinical dose range for olanzapine (10-20 mg/day) and samidorphan (5-20 mg/day), no significant correlation was noted between (a) olanzapine concentrations and change in PANSS total score, or % change in body weight, in patients treated with OLZ/SAM or olanzapine, and (b) samidorphan concentration or samidorphan-to-olanzapine concentration ratio and % change in body weight. No meaningful difference in olanzapine and samidorphan concentrations or samidorphan-to-olanzapine concentration ratios was observed between patients with <10% and ≥10% weight gain.

Conclusions. The antipsychotic efficacy of olanzapine was not affected by samidorphan at any concentration of olanzapine. Furthermore, olanzapine-associated weight gain did not correlate with olanzapine dose or plasma concentration. Finally, the effect of OLZ/SAM on mitigation of olanzapine-associated weight gain was not affected by intersubject variability in olanzapine and/or samidorphan plasma concentrations.

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Effect of the HP-3070 Transdermal System (Secuado) on Symptoms of Hostility in Adults with Schizophrenia

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Abstract

Background. Patients with schizophrenia may exhibit symptoms of hostility. HP-3070, a once-daily asenapine transdermal system, is the first antipsychotic patch approved by the FDA for use in adults with schizophrenia, and its efficacy in this indication has been demonstrated. This post hoc analysis of a phase 3 randomized study investigated the efficacy of HP-3070 in treating hostility in patients with schizophrenia.

Methods. In the pivotal phase 3 study, adults with schizophrenia were randomized 1:1:1 to once-daily treatment with HP-3070 3.8 mg/24 h, 7.6 mg/24 h, or placebo for 6 weeks. Least-squares mean (LSM) changes in the PANSS hostility item score (P7) and PANSS-Excited Component (PANSS-EC), the sum of items P4 (Excitement), P7 (Hostility), G4 (Tension), G8 (Uncooperativeness), and G14 (Poor impulse control), from baseline to week 6 were assessed post hoc. Efficacy was analyzed with a mixed-effects model for repeated measures (MMRM) adjusted for PANSS-positive symptoms, items P1 (Delusions), P2 (Conceptual disorganization), P3 (Hallucinatory behavior), P5 (Grandiosity), P6 (Suspiciousness/persecution), and G9 (Unusual thought content) and presence of somnolence (including hypersomnia, hypersomnolence, or sedation) or akathisia.

Results. Among the 369 patients with a baseline PANSS hostility item score >1 and hostility scores collected at both baseline and week 6 (126 HP-3070 7.6 mg/24 h; 123 3.8 mg/24 h; 120 placebo), the week 6 LSM (95% CI) change from baseline in PANSS hostility item score was significantly better with HP-3070 than placebo for 7.6 mg/24 h (−0.4 [−0.6, −0.2]; $P < .001$) and 3.8 mg/24 h (−0.3 [−0.6, −0.1]; $P < .01$). Similar results were observed after adjusting for covariates ($P < .01$ for both doses). The week 6 PANSS-EC LSM change from baseline was also greater for HP-3070 7.6 mg/24 h (−1.1 [−1.9, −0.4]; n = 164; $P < .01$) and 3.8 mg/24 h (−1.3 [−2.0, −0.6]; n = 168; $P < .001$) compared with placebo (n = 165).

Conclusions. In this post hoc analysis, HP-3070 was superior to placebo in reducing hostility in patients with schizophrenia, even after adjusting for covariates, suggesting that these effects are at least partially independent of general antipsychotic effects or of effects on sedation or akathisia. These findings suggest that HP-3070 may have a specific anti-hostility effect in patients with schizophrenia.

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