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A randomized, double-blind, placebo-controlled proof of concept study to evaluate samidorphan in the prevention of olanzapine-induced weight gain in healthy volunteers

Bernard L. Silverman [a,*], William Martin [a], Asli Memisoglu [a], Lauren DiPetrillo [a], Christoph U. Correll [b,c], John M. Kane [b,c]

[a] Alkermes, Inc., Waltham, MA, United States
[b] Hofstra Northwell School of Medicine, Hempstead, NY, United States
[c] The Zucker Hillside Hospital, Psychiatry, Glen Oaks, NY, United States

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ABSTRACT

Antipsychotic medications are associated with weight gain and adverse metabolic effects that complicate the treatment and management of schizophrenia. Olanzapine (OLZ) in particular is associated with significant weight gain and adverse metabolic effects. The present Phase 1, proof of concept, multicenter, randomized, double-blind, placebo-controlled study investigated the safety and effect on weight of a combination of OLZ (10 mg) and the opioid modulator samidorphan (SAM; 5 mg) in comparison to OLZ alone in healthy, male normal weight volunteers. Altogether, 106 male subjects with stable body weight and BMI 18–25 kg/m^2 were randomized to OLZ alone, OLZ + SAM, SAM alone, or placebo in a 2:2:1:1 ratio. The primary efficacy endpoint, mean (SD) body weight change from baseline to last assessment in the 3-week treatment period, was significantly less for OLZ + SAM vs. OLZ alone subjects [+2.2 (1.4) kg vs. +3.1 (1.9) kg; respectively; $p = 0.02$]. In contrast, there was no significant difference in weight from baseline for either SAM or placebo [+0.1 (1.0) kg and +0.8 (1.4) kg, respectively]; $p = 0.09$. Overall, OLZ + SAM compared to OLZ alone had similar safety and tolerability. In addition, less nausea was observed in subjects given OLZ + SAM compared to SAM alone. Thus, OLZ + SAM may offer effective treatment of schizophrenia with less weight gain and metabolic risk. Additional research exploring additional doses over longer durations in psychiatric populations is warranted.

1. Introduction

Nearly all antipsychotic medications are associated with weight gain and significant adverse metabolic effects including Type 2 Diabetes Mellitus (T2DM), hyperglycemia, and hyperlipidemia (Bak et al., 2014; Correll et al., 2011; De Hert et al., 2011b; Leucht et al., 2012; Liposits and Bohn, 1993). This adverse effect cluster presents an obstacle in the treatment and management of patients with schizophrenia or bipolar disorder, and limits patient adherence to medication and consequently adversely impacts treatment outcomes. Therefore, a medication that is effective in treating symptoms of schizophrenia and bipolar disorder with an improved safety and tolerability profile is a much needed addition to the therapeutic armamentarium.

Olanzapine (OLZ) is regarded as one of the most effective treatments for schizophrenia and bipolar disorder (Cipriani et al., 2011; Leucht et al., 2013), but concerns with weight gain and adverse metabolic effects have affected physician prescribing and patient adherence to OLZ treatment (De Hert et al., 2011a; Lieberman et al., 2005). However, several studies have demonstrated that patients actually stay on OLZ for longer periods of time and that it has a lower discontinuation rate in comparison with other antipsychotics. For instance, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (Lieberman et al., 2005) demonstrated that patients stayed on OLZ significantly longer than other antipsychotics (median time-to-discontinuation: 9.2 months vs. 3.5 to 5.6 months for comparators, with hazard ratios ranging from 0.63 to 0.78). The CATIE study specifically noted that OLZ had the "lowest rate of discontinuation due to lack of efficacy", as well as a "greater reduction in psychopathology, longer duration of successful treatment", and "lower rate of hospitalizations for an exacerbation of schizophrenia" compared with other approved antipsychotic drugs. Despite these benefits of OLZ, utilization has decreased due to the growing concern and awareness of OLZ-associated weight gain and metabolic dysregulation (Nasrallah and Newcomer, 2004). Indeed, in the CATIE study discontinuation from OLZ was primarily due to weight gain or metabolic effects (Lieberman et al., 2005).

* Corresponding author at: Alkermes, Inc., 852 Winter Street, Waltham, MA 02451, United States.
E-mail address: Bernard.silverman@alkermes.com (B.L. Silverman).

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A small pilot study in patients with schizophrenia or schizoaffective disorder suggests that the concomitant use of an opioid antagonist, naltrexone, may be beneficial at attenuating antipsychotic-associated weight gain (Tek et al., 2014). Although the precise mechanism of this attenuation is unknown, a reduction in cravings for sweet and rich foods was observed in patients receiving naltrexone compared to placebo. Samidorphan (SAM; previously referred to as RDC-0313 or ALKS 33) binds with high affinity to human μ-, κ-, and δ-opioid receptors and acts primarily as an antagonist at μ-opioid receptors, with low intrinsic activity at κ- and δ-opioid receptors (see Compound #1 (Wentland et al., 2009)). Nonclinical studies suggest that SAM may be useful in mitigating or preventing OLZ-induced weight gain. Using a standard rodent model, it was demonstrated that co-administration with SAM mitigated OLZ-induced weight gain, whereas naltrexone did not (Todtenkopf et al., 2010). In a subsequent study using nonhuman primates to investigate OLZ-induced changes in weight gain and metabolic effects, SAM attenuated OLZ-induced weight gain and abdominal fat accretion following 28 days of daily dosing (Todtenkopf et al., 2011). In the present Phase 1 proof of concept study, the mean change in body weight gain in healthy volunteers receiving OLZ (10 mg), OLZ + SAM (10 mg + 5 mg, respectively), SAM (5 mg), or placebo was assessed over 3 weeks. Data from these studies as well as clinical safety experience with samidorphan informed dose and ratio selection for the present trial where it was hypothesized that OLZ + SAM would be associated with significantly less weight gain than OLZ alone.

2. Experimental methods

The study was conducted at 3 sites in the United States between March 2012 and July 2012 in accordance with the Declaration of Helsinki, 1964 and Good Clinical Practice principles outlined in the International Conference on Harmonization, 1997. The protocol, amendments and informed consent were approved by an Institutional Review Board for each site, and written informed consent was obtained for all participants.

2.1. Study design

This was a multi-center, randomized, double-blind, double-dummy placebo- and active-controlled study with the primary aim to compare the change from baseline in body weight following 3 weeks of once-daily oral administration in healthy, normal weight male volunteers receiving OLZ + SAM and those receiving OLZ alone. Following the screening visit, eligible subjects underwent a 7- to 14-day baseline assessment to assess body weight stability. One hundred and six eligible, consenting, male subjects were randomized into the study at a 2:2:1:1 ratio to: OLZ (10 mg), OLZ + SAM [OLZ (10 mg) + SAM (5 mg)], SAM (5 mg), or placebo. The treatments were randomized and double-blind, with matching placebos for OLZ and SAM. During the 4-day inpatient period, study drug was administered daily by study staff and blood samples for pharmacokinetic analysis were collected. After discharge from the inpatient facility, subjects took the study drug daily on an outpatient basis for an additional 17 days, for a total treatment period of 21 days. Subjects returned to the clinic weekly after randomization for assessments and PK sampling. A follow-up visit occurred 14 days after the end of the treatment period.

2.2. Patient selection

Male subjects between the ages of 18 and 40 years old were eligible. Inclusion criteria were: a BMI of 18–25 kg/m^2 at screening, stable body weight (change ≤5% by history) for at least 3 months prior to screening and a change in absolute body weight of ≤1 kg between screening and randomization (7 to 14 days). Exclusion criteria were: history of diabetes or glucose intolerance, systemic corticosteroid use within 1 year prior to screening, clinically significant medical condition or observed abnormalities (including findings from physical examination, electrocardiogram [ECG], laboratory evaluation [particularly kidney or liver function test results], or urinalysis), clinically significant illness within 30 days before the first study drug administration, a history of dependence to any substance other than caffeine or nicotine, prior (within 6 months), active or planned involvement in a weight management program, a current psychiatric condition or prior use of any antipsychotic medication for a psychiatric condition.

2.3. Study assessments

2.3.1. Efficacy

Body weight was measured at baseline, prior to inpatient discharge and at every visit thereafter. For all body weight measurements, all subjects were weighed on the same scale under the same conditions wearing hospital gowns and removing all personal items prior to each body weight measurement. Additionally, subjects underwent venipuncture and blood sampling for the following parameters after at least 8 h of fasting: glucose, insulin, triglyceride levels and cholesterol.

2.3.2. Safety and tolerability

Adverse events (AEs) and serious adverse events (SAEs), vital signs and laboratory evaluations were monitored from screening through completion of the final study visit. All AEs occurring during that time period were followed until resolution, until deemed stable by the principal investigator, or until the subject was deemed lost to follow-up by the investigator. AEs and SAEs that had an onset after the safety follow-up were not collected nor reported unless the investigator deemed the event related to the study drug.

2.3.3. Pharmacokinetic assessments

Plasma OLZ and SAM concentrations were quantified by a previously validated LC/MS/MS method with a limit of sensitivity of 0.250 ng/mL for each analyte. Samples were collected at pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 7, 12, 16, and 24 h post-dose on the first dosing day, and 1, 2 and 6 h post-dose on the second dosing day. Pre-dose plasma samples were also collected at Visits 3, 4 and 5. The pharmacokinetic population was defined as all randomized subjects who received at least the first dose of study drug and who have at least one measurable concentration of any study drug or analyte. Pharmacokinetic parameters were calculated using noncompartmental analysis (NCA).

2.4. Data analysis plan

Sample size was based on the number of subjects on OLZ + SAM and on OLZ alone needed to evaluate the primary efficacy endpoint. A sample size of 30 subjects per group was estimated to provide 80% power to detect a 50% reduction in OLZ-induced weight gain (Mann-Whitney Wilcoxon test; 2-sided $\alpha = 0.05$) assuming mean (SD) weight gain of 2.0 (1.3) kg. The efficacy population included all randomized subjects who received at least one dose of study drug and at least one post-baseline weight assessment. The primary efficacy endpoint, absolute change from baseline in body weight (kg) following 21 days of treatment, was evaluated between subjects administered OLZ + SAM and subjects administered OLZ alone using a non-parametric method (i.e., Mann-Whitney-Wilcoxon test, two sided $\alpha = 0.05$). For the primary efficacy analysis, the last assessment in the treatment period was used for subjects who discontinued prior to the end of the 3 week treatment period. Additional exploratory analysis of the primary efficacy endpoint using the method above included the following comparisons: SAM vs. placebo; OLZ vs. placebo; OLZ + SAM vs. SAM; OLZ + SAM vs. placebo. Descriptive summaries and results of exploratory hypothesis testing were generated for additional efficacy endpoints, and included BMI, fasting glucose, fasting insulin, glucose to insulin ratio, triglyceride and cholesterol levels. Hypothesis testing was conducted using a non-parametric test (Mann-Whitney-Wilcoxon test, two-sided $\alpha = 0.05$),

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