Single- and Multiple-Dose Pharmacokinetic, Safety, and Tolerability Profiles of Olanzapine Long-Acting Injection: An Open-Label, Multicenter, Nonrandomized Study in Patients With Schizophrenia

Malcolm Mitchell, MBBS, MFPM[1]; Prajakti Kothare, PhD[1]; Richard Bergstrom, PhD[2]; Fangyi Zhao, PhD[1]; Kai Yu Jen, PhD[3]; Daniel Walker, PhD[1]; Jason Johnson, MS[1]; and David McDonnell, MB, MRCPsych[1]

[1]Lilly Research Laboratories, Indianapolis, Indiana; [2]Indiana University School of Medicine, Indianapolis, Indiana; and [3]PharmaNet/i3, Indianapolis, Indiana

ABSTRACT

Background: This was the first study, to our knowledge, in patients with schizophrenia in which olanzapine long-acting injection (LAI) was used to attempt delivery of depot formulation in multiple therapeutic doses.

Objective: This study assessed the safety profile, tolerability, and pharmacokinetic (PK) properties of olanzapine after single and multiple administrations of olanzapine LAI and evaluated maintenance of symptom control.

Methods: This was an open-label, multicenter, nonrandomized study of olanzapine LAI in patients with schizophrenia stabilized with oral olanzapine. Key inclusion criteria included well-tolerated and efficacious treatment with daily olanzapine. Patients were required to be receiving a stable oral dose for 4 weeks before study entry with no requirement for as-needed additional antipsychotic medication within 2 weeks before entry. Exclusion criteria included serious unstable illnesses, unresolved seizures, pregnancy or breast-feeding, hypothyroidism, hyperthyroidism, narrow-angle glaucoma, or serious suicidal risk. Initially, 34 patients received olanzapine LAI as a single injection of 50 to 450 mg, and as the study progressed, 247 patients received consecutive injections of 100 to 405 mg olanzapine LAI administered every 2, 3, or 4 weeks for 3 to 6 months. Spontaneously reported adverse events were recorded at each visit. Analyses of efficacy and safety profile parameters were performed on an intent-to-treat basis. All hypotheses were tested at a 2-sided significance level of $P < 0.05$.

Results: Study participants had a mean age of 39 years and were primarily white men. The PK properties suggested prolonged release providing sustained olanzapine plasma concentrations and supporting a dosing interval $\leq$4 weeks. Olanzapine LAI doses of 150 or 300 mg every 2 weeks and 210 or 405 mg every 4 weeks provide mean steady-state olanzapine concentrations similar to those after oral administration of 5 to 20 mg/d. The mean baseline Brief Psychiatric Rating Scale score of 17.27 decreased by 2.68 points, and the mean baseline Clinical Global Impression–Severity score of 3.39 decreased by 0.23 points, indicating that patients' psychiatric health was maintained or slightly improved. Significant mean weight gain ($P < 0.001$) and treatment-emergent changes in nonfasting glucose were observed. Incidence of weight gain $\geq$7% of baseline was observed in 17.8% of patients. The common adverse events were injection site pain, anxiety, sedation, insomnia, somnolence, and headache, and the safety profile for olanzapine LAI was comparable to that of oral olanzapine, except for injection site–related adverse events.

Conclusion: The safety profile and PK data from this study support continued clinical development of olanzapine LAI in controlled efficacy studies at doses $\leq$300 mg every 2 weeks or 405 mg every 4 weeks. Clinical trial registry ID: 4535 http://www.lillytrials.com/results/ZyprexaLAI.pdf. (*Clin Ther.* 2013;35:1890–1908)

Accepted for publication September 24, 2013.
http://dx.doi.org/10.1016/j.clinthera.2013.09.023
0149-2918/$ - see front matter

Key words: long-acting injection, olanzapine, pharmacokinetics, safety, schizophrenia, tolerability.

INTRODUCTION

Olanzapine is an atypical antipsychotic approved in the United States, Europe, and elsewhere as oral treatment for schizophrenia and bipolar I disorder. Many studies have found olanzapine effective in reducing both positive and negative symptoms[1] and improving physical functioning (as assessed with the Medical Outcomes Study 36-Item Short-Form Health Survey)[2,3] in patients with schizophrenia. Nevertheless, patients may become partially adherent or nonadherent to treatment. For antipsychotic medications in general, approximately 24% of patients with schizophrenia will be nonadherent with their treatment regimen.[4] Nonadherence can occur for a variety of reasons, including substance abuse, symptom severity, and tolerability issues, such as weight gain and extrapyramidal symptoms. Treatment nonadherence usually leads to psychotic relapse,[5] subsequent hospitalization,[6] and increased social and economic burdens.[7,8]

Recent studies with risperidone long-acting injection (LAI) formulation suggest better adherence rates than with oral antipsychotics.[9,10] Olanzapine LAI was developed to allow patients receiving olanzapine to benefit from potentially better adherence rates of LAI formulations. Such a long-acting formulation of olanzapine was considered valuable in patients who have difficulty remaining adherent to oral antipsychotics or depot formulations of typical antipsychotics.

A previously developed formulation, intramuscular (IM) olanzapine, which is administered as a solution, results in rapid absorption and produces peak plasma concentrations within 15 to 45 minutes. After a single dose, exposure AUC of this IM product is equivalent to that after an oral dose, except a substantial portion of AUC occurs much more rapidly after injection. Correspondingly, this rapidly absorbed IM formulation of olanzapine was developed to treat extremely agitated patients diagnosed as having bipolar mania[11] or schizophrenia.[12]

In contrast, to achieve the objectives and advantages of olanzapine LAI, it was necessary to intentionally and substantially slow the rate of olanzapine absorption from an IM injection site. Clinical testing of a salt of olanzapine with extremely low solubility was performed; the result was the olanzapine LAI formulation that is composed of a suspension of olanzapine pamoate, the salt of pamoic acid and olanzapine base. Desirable properties for a depot IM formulation include a sustained exposure to drug without an initial lag time when no drug is released. An initial clinical pharmacokinetic (PK) study of olanzapine LAI at low, single doses of 10 to 40 mg in healthy individuals confirmed that IM injection of olanzapine LAI provided immediate systemic exposure occurring within minutes to hours after injection and sustained olanzapine concentration lasting for days to weeks after the injection.[13] A further study was required to assess the effects of both higher single doses and the safety profile, tolerability, efficacy, and PK properties of higher therapeutic doses of olanzapine LAI given at an interval no more frequently than every 2 weeks.

In addition, it was important to ascertain the pharmacologic properties of a depot atypical antipsychotic such as olanzapine LAI to assess whether such a formulation could provide a consistent PK profile that would be at least comparable to the profile that can be achieved by compliant oral dosing.

The present study was a Phase IB open-label study that assigned patients with schizophrenia taking stable doses of oral olanzapine to either single or multiple doses of olanzapine LAI administered every 2, 3, or 4 weeks for up to 24 weeks of treatment. This protocol was conducted in 2 main phases: single dose and multiple dose. The proposed doses and intervals for olanzapine LAI in the multiple-dose phase were to be selected based on clinical tolerability data and PK data from the single-dose phase of this study. The maximum dose would not exceed 450 mg because this would represent a dosing volume of 3 mL. The 3-mL dosing volume limit was based on market research results that indicated that routine administration volumes of up to 3 mL would be acceptable for longer periods. During the single-dose phase, the decision to either increase or decrease the dose for each subsequent group of individuals was made by the sponsor after reviewing the tolerability, safety profile, and olanzapine plasma concentration data of the previous group. All doses were confirmed in writing with the investigator before being administered to the next group. During the multiple-dose phase, doses of LAI olanzapine could vary, depending on tolerability, PK data of previous injections, incoming data from the single-dose phase, and the clinical status of the patient.