2. HGLQ Synopsis

Clinical Study Report Synopsis: Study F1D-MC-HGLQ

Title of Study: A Randomized, Open-Label Study Comparing the Effects of Olanzapine Pamoate Depot with Oral Olanzapine on Treatment Outcomes in Outpatients with Schizophrenia	
Number of Investigator(s): This multicenter study included 59 principal investigator(s).	
Study Center(s): This study was conducted at 59 study centers in 11 countries.	
Publication(s) Based on the Study: Detke H, McDonnell D, Andersen S, Watson S. Olanzapine long-acting injection in patients with schizophrenia at risk of relapse: 12-week switching data. Eur Neuropsychopharmacol. 2008;18(Suppl 4):S435. Detke HC, Zhao F, Andersen SW, Watson SB, McDonnell DP. Comparison of olanzapine long-acting injection switching methods: an 8-month analysis of patients with schizophrenia at risk of relapse. Poster presented at the New Clinical Drug Evaluation Unit, Hollywood, Florida, June 29-July 2, 2009.	
Length of Study: Date of first patient enrolled: 04 May 2006 Date of last patient completed: 29 September 2009	**Phase of Development:** 3b
Objectives: The primary objective of this study was to assess the time to all-cause discontinuation in outpatients with schizophrenia who are at risk for relapse, as demonstrated by at least two episodes of clinical worsening in the past 24 months such that the patient was hospitalized or required an increased level of care surrounding the episode. Patients were treated with either olanzapine pamoate depot (OP Depot) or oral olanzapine for up to 104 weeks of treatment. Superiority between these two groups was assessed by comparing the log-rank statistic from the Kaplan-Meier survival analysis. Secondary objectives were to assess the differences between OP Depot and oral olanzapine on: • health outcome measures using the Heinrich-Carpenter Quality of Life in Schizophrenia Scale (QLS), Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), EuroQol 5 Dimensions Questionnaire (EQ-5D), Burden Assessment Scale (BAS), Resource Utilization, Hospitalization Inventory, Scale to Assess Unawareness of Mental Disorder (SUMD), Working Alliance Inventory (WAI), Schizophrenia Objective Functioning Instrument (SOFI), Patient Satisfaction with Medication Questionnaire-Modified (PSMQ), and Drug Attitude Inventory (DAI) • the incidence of all-cause discontinuations • the time to relapse • the incidence of patients experiencing a relapse • the change from baseline to endpoint on the Clinical Global Impression – Severity of Illness (CGI-S), Positive and Negative Syndrome Scale (PANSS) Total and Subscale scores, and the Brief Psychiatric Rating Scale • the safety and tolerability of treatment.	
Study Design: A multicenter, global, Phase 3b, open-label, randomized study comparing the treatment effectiveness and safety of OP Depot with oral olanzapine in the treatment of outpatients with schizophrenia.	
Number of Patients: Planned: 520 (260 OP Depot; 260 oral olanzapine) Randomized: 524 (264 OP Depot; 260 oral olanzapine) Completed: 243 (119 OP Depot; 124 oral olanzapine)	

Approval Date: 22-Dec-2011 GMT

Diagnosis and Main Criteria for Inclusion: Males and females aged 18 to 65 years who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (or text revision 2000) criteria for schizophrenia and had experienced at least two episodes of clinical worsening of schizophrenia symptoms in the past 24 months such that hospitalization or an increased level of care surrounding the episode was required. Patients also had a CGI-S score ≤4 at Visits 1 and 2, had a PANSS Total score <70 at Visits 1 and 2, had an unsatisfactory clinical response or experienced adverse events (AEs) or were nonadherent on current antipsychotic therapy such that the patient and the treating physician desired to change the patient's therapy, and were outpatients with no hospitalization in the 8 weeks prior to study entry.
Study Drug, Dose, and Mode of Administration: Olanzapine pamoate depot (OP Depot) 150 to 405 mg/4 weeks, given as deep intramuscular injection of suspension in aqueous vehicle.
Reference Therapy, Dose, and Mode of Administration: Oral olanzapine 5 to 20 mg/day given as 5-mg oral tablets.
Duration of Treatment: Open-label treatment phase lasting up to 104 weeks
Variables: Efficacy: Time to and incidence of all-cause discontinuation; incidence and time to relapse; PANSS Total and subscales; CGI-S. Safety: Adverse events; vital signs; weight; laboratory analytes; electrocardiograms (ECGs); extrapyramidal symptoms (EPS) using the Barnes Akathisia Scale, Simpson-Angus Scale, and Abnormal Involuntary Movement Scale; 3-hour postinjection safety observations. Health Outcomes: QLS, SF-36, EQ-5D, BAS, Resource Utilization, Hospitalization Inventory, SUMD, WAI, SOFI, PSMQ, and DAI.

Statistical Evaluation Methods:

All analyses were conducted on an intent-to-treat basis. Efficacy analyses included all randomized patients with baseline and postbaseline observations unless otherwise stated. Analysis of time to all-cause discontinuation, which was the primary objective, excluded discontinuations due to Sponsor decision in order to minimize bias. All time-to analyses were conducted using Kaplan-Meier methodology, with between-group comparisons conducted using the log-rank test. All baseline-to-endpoint analyses were conducted using last-observation-carried-forward (LOCF) methodology. Baseline-to-endpoint changes in efficacy and health outcomes measures were also assessed using repeated measures methodology. Analysis of variance (ANOVA) models were used to evaluate continuous data and generally included terms for treatment and investigator. The analysis of covariance (ANCOVA) on the LOCF change from baseline to endpoint in PANSS Total score included baseline PANSS Total score as a continuous covariate as well as terms for treatment and investigator. Type III sums of squares were used to test for significant effects for all ANOVA/ANCOVA models. For analysis of proportion, Fisher's exact test was used unless otherwise specified. All efficacy and safety hypothesis tests were conducted at a two-sided 0.05 significance level.

Switching to OP Depot: Two interim analyses were conducted during the study to compare switching methods within the OP Depot treatment group. The results of these analyses were not intended to change the conduct of the study and had no impact on the overall study results. The first analysis, per protocol, was conducted after 12 weeks of treatment with OP Depot and compared 4 switching groups (direct switch without oral olanzapine supplementation, direct switch with oral olanzapine supplementation, taper without supplementation, and taper with supplementation) on time to all-cause discontinuation, as well as major safety and efficacy measures. A second interim analysis was conducted after 8 months of treatment with OP Depot and compared 2 switching groups (direct switch and taper, regardless of oral olanzapine supplementation) on the same measures as the previous interim analysis.

Health Outcomes: Frequencies were compared using Fisher's exact test. Means were compared using an ANCOVA model (including terms for investigator, treatment, and baseline) and a likelihood-based repeated-measures analysis conducted on the postbaseline change scores. The linear model for this repeated-measures analysis included terms for baseline, treatment, investigator, visit, and treatment-by-visit interaction. For the resource and hospital utilization, the incidence and mean number of hospitalization days were calculated with the associated 95% confidence interval for each treatment.

Summary: Study F1D-MC-HGLQ was a large, randomized, open-label trial designed to assess the treatment effectiveness and safety of OP Depot for up to 2 years of treatment compared with oral olanzapine in outpatients with schizophrenia who were at risk for relapse. The primary measure of treatment effectiveness was time to all-cause discontinuation. It should be noted that a 3-hour postinjection observation period, additional safety assessments, and other risk minimization requirements were added midway through the study and applied only to the OP Depot treatment group.

Disposition and Baseline Characteristics: A total of 524 patients were randomized to OP Depot (n=264) or oral olanzapine (n=260). Patients were predominantly male (67.2%) and Caucasian (62.0%), with a mean age of 41 years. Mean PANSS Total score was 57, and mean CGI-S score was 3.3, indicating a mildly ill patient population at baseline. Mean number of episodes of schizophrenia in the previous 24 months was 2.7, with approximately 41% of patients having been hospitalized at least once during this time. However, only 17% of patients had been psychiatrically hospitalized in the 6 months prior to study entry. Also, only 4.6% of patients were rated as nonadherent to their treatment regimen in the month prior to study entry, suggesting that the patient sample was relatively adherent and not particularly at risk for relapse. No statistically significant differences were observed between treatment groups with respect to baseline characteristics. The average daily dose of oral olanzapine was 13 mg. The average monthly dose of OP Depot was 387 mg, with most patients continuing to receive 405 mg/4-weeks throughout their study participation. A total of 47% of randomized patients completed the 2-year study (45% OP Depot, 48% oral olanzapine, p=.599).

Efficacy: The study did not achieve its primary objective as the OP Depot and oral olanzapine treatment groups did not differ significantly on time to all-cause discontinuation. Median time to discontinuation was similarly long for both treatment groups (645 days OP Depot versus 678 days oral olanzapine, p=.612). Rate of relapse (20.1% OP Depot versus 18.5% for oral olanzapine, p=.659) and time to relapse (539 days OP Depot versus 624 days oral olanzapine, p=.585) also did not differ significantly between groups. Both groups showed similar maintenance of clinical stability on the measures of symptomatology, with mean PANSS Total scores remaining in the 50s throughout the 2-year study. Because the 405 mg/4-weeks OP Depot dose provided approximately 15 mg/day of olanzapine, whereas the oral olanzapine group could be dosed to 20 mg/day, an exploratory post-hoc analysis was conducted to test the impact of this difference in allowed dose range on treatment outcomes. When dose increases to 20 mg/day after the initial 8 weeks of treatment (the switching period) were treated statistically as a subacute relapse, the OP Depot group had a longer median time to relapse (539 days OP Depot versus 281 days oral olanzapine, p<.001) and a lower relapse rate (20% OP Depot versus 40% oral olanzapine, p<.001) than the oral olanzapine group, thus demonstrating that the difference in maximum allowed dose likely impacted the between-group effectiveness results for the study.

Methods of switching were also analyzed as investigators could opt to switch patients directly to study drug or could concomitantly taper patients' previous antipsychotic medication during the first 2 weeks of treatment. Investigators could also opt to supplement patients with up to 5-mg/day oral olanzapine from Week 2 through Week 8. For patients switched to OP Depot, 57% were switched directly and 43% were concomitantly tapered. Most OP Depot patients (81%) did not receive any supplemental oral olanzapine, although oral olanzapine supplementation occurred more often among patients who had been tapered (28%) than among those who switched directly (12%). Analyses indicated no clear advantage of any one switching method over another with regard to subsequent treatment effectiveness or safety.

Health Outcomes: Findings from the various health outcomes and quality-of-life assessments (SF-36, QLS, DAI, WAI, SOFI, SUMD, PSMQ, EQ-5D Questionnaire, BAS, Resource Utilization, and Hospitalization Inventory) in general revealed overall improvement from baseline in both treatment groups over the 2-year study, with no significant overall between-group differences on any of the health outcomes measures, except for hospitalized duration for psychiatric purposes. Incidence of postbaseline psychiatric hospitalization was low for both the OP Depot and oral olanzapine treatment groups (7.6% and 9.2%, respectively), but mean duration of hospitalization was significantly longer for the oral olanzapine group (1.80 days [mean of 20 days for those hospitalized]) compared with the OP Depot group (0.43 days [mean of 6 days for those hospitalized], p=.020).

Safety: Overall safety findings indicated comparable safety and tolerability between OP Depot and oral olanzapine. Analysis of AEs, laboratory analytes, vitals, weight, ECGs, and EPS consistently found few statistical differences and no clinically meaningful differences between the OP Depot treatment group and the oral olanzapine treatment group on any of these measures. These findings indicate that OP Depot has a safety profile comparable to that of oral olanzapine.

Among all randomized patients, the most frequently reported treatment-emergent adverse events were weight increased (17%), insomnia (11%), somnolence (9%), and anxiety (9%), with no statistically significant differences between groups. Fifty-nine patients (11.3%) experienced a serious adverse event. There were 2 deaths in the study, both in the oral olanzapine treatment group and both reported as unrelated to study drug. No postinjection delirium/sedation syndrome events were reported, and few AEs of any kind were noted during the 3-hour postinjection period. Incidence of injection-related AEs was low (6% of OP Depot patients).

No statistically significant differences were seen between treatment groups in metabolic changes. Patients in both treatment groups gained an average of 2 kg (SD 7 kg), with 41% of OP Depot patients and 38% of oral olanzapine patients gaining ≥7% of their baseline weight.

Analysis of EPS indicated low rates (0% to 4%) at any time in the study for either treatment group. No differences were seen between the OP Depot and oral olanzapine treatment groups in Parkinsonism, akathisia, and dyskinetic movements.

Conclusions: OP Depot admininstered every 4 weeks was found to be as effective, tolerated, and safe as daily treatment with oral olanzapine in patients with schizophrenia for up to 2 years of treatment. Time to all-cause discontinuation for OP Depot was similar to that of oral olanzapine, despite the 3-hour postinjection observation period and other precautionary procedures that were added during the course of the study to the OP Depot treatment group only.