# 2. HGKB Synopsis

# Clinical Study Report Synopsis: Study F1D-MC-HGKB

**Title of Study:** An Open-Label Study of Intramuscular Olanzapine Depot in Patients with Schizophrenia or Schizoaffective Disorder

**Number of Investigator(s):** This multicenter study included 127 principal investigator(s).

**Study Center(s):** This study was conducted at 127 study centers in 25 countries.

**Publication(s) Based on the Study:**

McDonnell DP, Kryzhanovskaya LA, Zhao F, Detke HC, Feldman PD. Comparison of metabolic changes in schizophrenia during randomized treatment with intramuscular olanzapine long-acting injection versus oral olanzapine. *Hum Psychopharmcol.* 2011;DOI: 10.1002/hup.1225 [Epub ahead of print].

McDonnell DP, Andersen SW, Detke HC, Zhao F, Watson SB. Long-term safety and tolerability of open-label olanzapne long-acting injection in the treatment of schizophrenia: 190-week interim results. *Clin Med Insight Psych.* 2011;3:37-47.

Ascher-Svanum H, Peng X. Montgomery W, Faries DE, Lawson AH, Witte MM, Novick D, Jemiai N, Perrin E, McDonnell DP. Assessing the infrequent oral supplementation of olanzapine long-acting injection in the treatment of schizophrenia. *Eur Psych*. 2011;26:313-319.

McDonnell DP, Detke HC, Zhao F, Watson SB, Gulliver AH. Long-term open-label safety of olanzapine long-acting injection: 190-week interim results. Poster presented at the American Psychiatric Association, San Francisco, California, 16-21 May 2009.

Detke HC, McDonnell DP, Andersen, SW, Watson SB. 160-week interim results from an open-label extension trial of olanzapine long-acting injection. *Int J Neuropsychopharmacol.* 2008;11(suppl 1):151.

| **Length of Study:** | **Phase of Development:** 3 |
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| Date of first patient visit: 30-August-04<br>Date of last patient visit: 31-December-10 | |

**Objectives:** The primary objective of Study F1D-MC-HGKB (HGKB) was to assess the long-term safety of olanzapine pamoate (OP) Depot in patients diagnosed with schizophrenia or schizoaffective disorder by monitoring laboratory values, vital signs, electrocardiograms (ECGs), adverse events (AEs), and extrapyramidal symptoms (EPS).

The secondary objectives of this study are as follows:

- To assess long-term efficacy of OP Depot in patients diagnosed with schizophrenia or schizoaffective disorder by measuring Positive and Negative Syndrome Scale (PANSS) total, PANSS positive, PANSS negative, and PANSS General Psychopathology Subscales, and Clinical Global Impressions-Severity of Illness (CGI-S).
- To assess long-term impact of OP Depot on quality of life (QoL) in patients diagnosed with schizophrenia or schizoaffective disorder, as measured by the Heinrichs-Carpenter Quality of Life Scale (QLS), Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), Resource Utilization, Hospitalization Inventory, Subjective Well-being under Neuroleptic Treatment-Short Form (SWN-S), and Patient Satisfaction with Medication Questionnaire (PSMQ)-Modified
- To further assess the long-term safety of OP Depot in patients diagnosed with schizophrenia or schizoaffective disorder as measured by the Columbia Suicide Severity Rating Scale (C-SSRS)
- To characterize the pharmacokinetics of OP Depot during long-term treatment

**Study Design:** Study HGKB was a Phase 3, open-label study designed to assess the long-term safety and efficacy of OP Depot (45 mg to 405 mg OP Depot) at a 2-, 3-, or 4-week interval) in patients who met the diagnostic criteria for schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) or DSM-IV text revision (DSM-IV-TR) 2000.

**Number of Patients**:
Planned: 700-1500
Randomized: Not applicable. Study F1D-MC-HGKB was a single-arm, open-label study.
Treated (at least 1 dose): 931 OP Depot
Completed: 370 (39.7%)

**Diagnosis and Main Criteria for Inclusion:** Key inclusion/exclusion criteria ensured that patients were men or women at least 18 years and no older than 76 years of age at time of consent; presented with schizophrenia that meets disease diagnostic criteria as defined in DSM-IV or DSM-IV-TR Sections 295.10, 295.20, 295.30, 295.60, or 295.90, or schizoaffective disorder (295.70), at the time of study entry; and previous completion (within 10 days) of another OP Depot study, if permitted by that study's protocol.

**Study Drug, Dose, and Mode of Administration:** Study drug was provided in sterile, pre-filled, 5-mL glass vials. Each vial contained OP monohydrate equivalent to 210, 300, or 405 mg olanzapine. In addition, 3 mL of sterile vehicle was provided in 5 mL single-use vials. Once the study drug was in the syringe, it was to be injected immediately into the patient's buttock.

**Reference Therapy/Comparator, Dose, and Mode of Administration:** Not applicable. Study F1D-MC-HGKB was a single-arm, open-label study.

**Duration of Treatment:** Maximum study duration was 6 years and 4 months. Mean individual patient exposure was 1073.4 days (2.9 years). Longest individual patient exposure was approximately 6 years.
**OP Depot Frequency:** 2-, 3-, and 4-week-interval dosing. Patients who were receiving study drug at 2- or 3-week intervals and were clinically stable were moved to a 4-week dosing interval.

**Variables:**
Efficacy: PANSS Total, PANSS Positive, PANSS Negative, PANSS General Psychopathology subscales, and CGI-S scores were assessed.
Bioanalytical: Plasma concentrations of olanzapine were determined using a validated bioanalytical assay.
Pharmacokinetic/Pharmacodynamic: Study HGKB provided 3844 plasma olanzapine concentrations collected from 377 patients for the duration of their participation in the study.
Health Outcomes: The SF-36, QLS, and SWN-S scales were administered during the study. Totals and subtotals from these scales included the SF-36 domains, the QLS total score and 4 factor scores, and the total and 5 subscales of the SWN-S. The changes from baseline in these totals and subtotals were summarized. Additionally, the PSMQ-Modified was summarized by item at endpoint. Resources used were summarized over the course of the study. Outpatient medical resource use was computed by units of outpatient medical resources consumed per patient-month of exposure to the treatment.
Safety: Treatment-emergent adverse events (TEAEs), laboratory analytes, vital signs, ECGs, and EPS rating scales were summarized.

**Statistical or Other Evaluation Methods:**
Safety: All patients who received at least 1 injection were included in the primary safety analyses. A baseline measure was the Visit 1 observation. A patient's endpoint measure was defined as his/her last measure in the study. Since this was an open-label study, only descriptive statistics of all relevant parameters were performed.
Efficacy: All total scores from rating scales and subscales were derived from the individual items. If any of the individual items were missing, the total scores were treated as missing. No adjustments for covariates were planned for this study. For the analysis of continuous measures, missing data was handled using last observation carried forward (LOCF) change from baseline to endpoint analyses. All total scores from rating scales and associated subscales were derived from individual items. If any of the individual items was missing, the total score was treated as missing. Because this was an open-label, non-randomized study, pooling study sites, analyses by individual study sites, and adjustments for multiple comparisons were not necessary.
Pharmacokinetic: Steady-state olanzapine concentrations were normalized by dividing an individual's measured olanzapine concentration at each visit by the total dose of olanzapine administered over the dosing regimen. A graphical and descriptive statistics summary was conducted to assess the average and range of drug concentrations and drug accumulation during each of the OP Depot dosing regimens. .

Health Outcomes: Mean number of outpatient resources used and the proportion of patients using outpatient resources were summarized. For those patients using outpatient resources, the mean number and standard deviation of outpatient resources used were examined. Hospitalizations were summarized over the course of the study. The aggregate number of days spent in the hospital per patient-year of exposure to treatment were computed. The summary included the mean number of hospital days, the proportion of patients with hospitalizations, and the mean length of stay per hospital admission.

**Summary:** The primary objective of this open-label study was to assess the long-term safety of OP Depot (which is also known as olanzapine long-acting injection) in patients diagnosed with schizophrenia (n=909 [98%]) and schizoaffective disorder (n=22 [2%]). A total of 931 patients entered the study and the mean age was 39.3 years (range: 18 to 74 years); 629 (67.6%) patients were Caucasian; and 621 (66.7%) patients were male. Patients had completed a previous OP Depot study (Studies F1D-MC-HGJZ, F1D-MC-HGKA, or F1D-EW-LOBS). To allow treatment consistent with standard medical practice, patients were permitted to receive supplementation of their treatment with oral olanzapine up to 20 mg/day. A total of 294 (31.6%) patients received supplemental oral olanzapine at some time during the study (mean dose 0.66 mg per day in those that received supplementation). Concomitant medications used included benzodiazepine in 348 (37.4%) patients and anticholinergics in 96 (10.3%) patents.

*Secondary Efficacy Measures:* Efficacy analyses were carried out to evaluate the maintenance of the treatment effect from previous OP Depot studies. The last observation carried forward (LOCF) change analysis from baseline was performed for PANSS total score and subscales and no clinically significant changes in total score subscales. Review of the individual items of the PANSS score demonstrated statistically significant changes from baseline to endpoint existed for active social avoidance (mean change = -0.11; p=.003), mannerisms and posturing (mean change = -0.09; p<.001), poor impulse control (mean change = 0.11; p<.001), and suspiciousness (mean change = 0.08; p=.038). The CGI-S scores demonstrated significant improvement after the third weekly visit from baseline (p<.001).

*Health Outcomes:* Overall, patients maintained their baseline level of functioning (which improved following initiation of OP Depot treatment in the previous 3 studies) or showed further improvement in their functional status. The use of outpatient services reflected the relatively stable nature of patients' clinical status and varied from 5.15 psychiatric visits per-patient-year of exposure to 0.03 per-patient-year of exposure for use of emergency room visits for psychiatric purposes. A total of 27.4% of patients were hospitalized over the course of the study, with 13 days of psychiatric hospitalization per patient year of exposure. The PSMQ-Modified demonstrated that 73.2% of patients were somewhat or were very satisfied with the current depot medication, 66.8% preferred or much preferred OP Depot treatment compared to last oral medication and 73.3% of patients thought that OP Depot use resulted in fewer or much fewer side effects.

*Pharmacokinetic Findings:* Typically, sparse blood samples for olanzapine concentration were obtained from each patient over the course of a year. Because of the long-term, flexible, dose-ranging nature of this study, plasma olanzapine concentrations were assessed for a variety of dosing conditions, resulting in a high level of variability in concentrations. As a result, the descriptive pharmacokinetic analysis was aimed at gaining a high-level understanding of general pharmacokinetic properties of OP Depot. Only 9 of the measured concentrations were below the limit of quantitation, even though the majority of samples were collected toward the end of the injection interval, thus suggesting that plasma concentrations were maintained throughout the end of the dosing interval, regardless of dosing regimen used. There was a clear trend toward increasing concentration with increasing OP Depot dose; however, the large variability in concentrations at any given dose resulted in a large overlap in concentrations between doses. When the overall concentration distributions were examined for each OP Depot dosing regimen, only the 300-mg/2-weeks regimen resulted in a sizable number (more than 10%) of concentrations that exceeded the upper end of the oral reference range (68.8 ng/mL). Minimal accumulation occurs for OP Depot for various dosing regimens over the course of up to 6 years.

*Safety Findings:* All 931 patients who entered the Open-Label Phase were evaluated for safety. Overall exposure was 2735.89 patient years. A total of 11 deaths, including 1 suicide, were reported during the study (acute heart failure, myocardial ischemia, myocardial infarction, road traffic accident, pneumonia, leptospirosis, hypertrophic cardiomyopathy, renal cell carcinoma, essential hypertension, and suicide). The types of AEs observed in the open-label phase for patients receiving OP Depot were generally consistent with the known safety profile of olanzapine. A total of 170 (18.3%) patients experienced serious adverse events (SAEs). The most frequently reported SAEs were schizophrenia, reported by 35 (3.8%) patients, and psychotic disorder, reported by 20 (2.1%) patients. During the course of the study there were 36 post-injection delirium sedation syndrome (PDSS) events in 35 patients identified. A total of 88 (9.5%) patients discontinued because of AEs. The most frequent AEs resulting in discontinuation were schizophrenia (15 [1.6%] patients), weight increased (8 [0.9%] patients), and psychotic disorder (7 [0.8%] patients).

**Conclusions:**

- This long term, open-label, multi-dose study in patients predominantly diagnosed with schizophrenia, demonstrated the safety of OP Depot generally consistent with the known safety profile of oral olanzapine, except for the events associated with the method of administration (PDSS events and injection site AEs). The PDSS events identified presented with symptoms consistent with an overdose of olanzapine and all patients fully recovered from these symptoms.
- While efficacy should be interpreted with caution in this open-label study, patients receiving OP Depot showed small changes in Total PANSS Scores and CGI-S Scores suggesting that OP Depot was effective in long-term maintenance of treatment effect. Patients' baseline level of functioning improved over the course of the study. Improved social functioning was consistently reported by both the clinicians and the patients and accompanied by an increase in patients' social integration in the community. Overall, the majority of patients were satisfied with their treatment with OP Depot.
- Olanzapine plasma concentrations were sustained over the dosing intervals, were within an acceptable range of concentrations observed historically for oral olanzapine, were proportional to the OP Depot dose over the wide dose range tested, and did not accumulate with long-term treatment. Pharmacokinetic analyses revealed no indication of long-term systemic accumulation of olanzapine, even after 6 years of treatment.