European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/608654/2008

ASSESSMENT REPORT

FOR

ZYPADHERA

International Nonproprietary Name: olanzapine

Procedure No. EMEA/H/C/000890

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 27 June 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for ZYPADHERA through the centralised procedure under "automatic access" as a substance already approved via the centralised procedure (olanzapine), based on the assumption that the pamoate salt form does not differ from olanzapine with respect to safety and efficacy. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 22 February 2007.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The applicant applied for the following indication: treatment and maintenance treatment of schizophrenia.

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 17 December 1999, 17 December 2000 and 23 October 2003. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pirjo Laitinen-Parkkonen
Co-Rapporteur: Pierre Demolis

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 27 June 2007.
- The procedure started on 20 July 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 October 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 October 2007.
- During the meeting on 12-15 November 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 16 November 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 January 2008.
- The summary report of the inspections carried out at the following sites
  - BeamOne, LLC, 9020 Activity Road Suite D, 92126 San Diego, California, USA,
  - BeamOne, LLC, 500 West 4th Street, 45804, Lima Ohio, USA

  between 12-15 May 2008, and
  - Eli Lilly and Company, Lilly Technology Center, Building 107, Indianapolis, Indiana, USA

  between 6-12 May 2008 was issued on 6 June 2008

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 March 2008.
- During the CHMP meeting on 17-19 March 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 27 June 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 9 July 2008.
- During the CHMP meeting on 21-24 July 2008, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant .
- The applicant submitted the responses to the second CHMP list of outstanding issues on 22 August 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second list of outstanding issues to all CHMP members on 12 September 2008.
- During the meeting on 22-25 September 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to ZYPADHERA on 25 September 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 24 September 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Olanzapine, a thienobenzodiazepine derivative (selective monoaminergic antagonist), is an atypical antipsychotic developed by Eli Lilly and Company (Lilly). Oral olanzapine for the treatment of schizophrenia received United States (US) Food and Drug Administration (FDA) approval 30 September 1996 and European Union (EU) approval on 27 September 1996. Oral olanzapine is also indicated for the treatment of acute mixed or manic episodes associated with bipolar I disorder. Additionally, a rapid-acting intramuscular (RAIM) injection formulation of olanzapine, indicated for agitation associated with schizophrenia and bipolar I mania, received approval in the US on 29 March 2004 and in the EU on 2 July 2001. The current application is for a depot formulation of olanzapine: olanzapine pamoate monohydrate (the salt of pamoic acid and olanzapine), suitable for deep intramuscular (IM) injection. Olanzapine Pamoate (OP) Depot consists of olanzapine pamoate monohydrate powder, which is suspended in an aqueous vehicle immediately prior to use. Non compliance is an important issue with schizophrenic patients, and abrupt withdrawal of treatment can lead to dramatic consequences. The Depot formulation has been developed to improve compliance in schizophrenic patients.

The initially sought indication was

Treatment of schizophrenia. ZYPADHERA is effective in the treatment of patients who have previously been exposed to oral olanzapine.

Maintenance treatment of schizophrenia. ZYPADHERA is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response to oral olanzapine.

However, further to discussion with the CHMP (see Discussion on Efficacy), the applicant agreed to change the indication to

Maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

2.2 Quality aspects

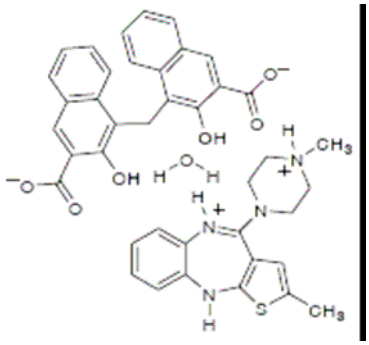
Introduction

This product has been developed as a sterile powder with viscous vehicle and is intended for intramuscular injection.

Active Substance

Olanzapine pamoate monohydrate (INN: olanzapine) exists as a yellow solid. Physico-chemical properties such as solubility (very low in most solvents), pKa, melting point have been adequately detailed.

Several hydrated forms of olanzapine pamoate have been identified including the monohydrate crystal form (commercial form) and two different non- stoichiometric hydrates.
Thermogravimetric analysis and solid-state NMR spectroscopy were used to determine the presence of water or solvent, and to calculate the hydrate or solvate stoichiometry. X-ray analysis allowed to differentiate the monohydrate from the non-stoichiometric hydrate and dehydrate forms and to confirm that the active substance is only found as the monohydrate crystal form. Based on thermal analysis, the dehydration of olanzapine pamoate occurred at high temperature (above 100C) indicating the water of crystallisation is strongly bonded.



- Manufacture

The synthesis of the active substance consists of the formation of the salt, starting from olanzapine and pamoic acid, followed by crystallisation, drying and milling to the desired particle size, and mixing in a blender to achieve the active substance, olanzapine pamoate monohydrate.

Suitable specifications are presented for starting materials, solvents and reagents as well as critical process parameters (CPPs) and in-process controls. Critical process parameters (CPPs), are parameters which are known or expected to affect the critical quality attributes of the active substance.
The proven acceptable ranges (PAR) have been determined using development experience. Since the crystallization is a one-step process, there are no intermediates.

During manufacturing process development, the following quality attributes for the active substance were studied: crystal form, particle size distribution, purity/impurity profile.
A Quality by Design Approach for the development program was retained and the development was focused on the robustness and control of the method of manufacturing.
The chemical structure has been fully elucidated using adequate methods including nuclear magnetic resonance spectroscopy (NMR), mass spectroscopy (MS), elemental analysis, X-ray crystallography, and X-Ray Diffraction (XRD). The structure of the active substance was also based on the route of synthesis.

The proposed approach to control and qualify the impurities was considered adequate. A comprehensive impurity profile was described. Origin of the synthesis related impurities and reaction pathways of the major degradation products were properly discussed. The level of impurities was satisfactorily controlled.

- Specification

Satisfactory specification for the active substance included parameters such as identification (IR and HPLC), identification of the crystal form (X-Ray), assay (HPLC), related substances (HPLC), residual solvents (GC), sulphated ash (Ph.Eur.), appearance, water content (Karl-Fisher), particle size (laser method), specific surface area (Nitrogen Adsorption), bacterial endotoxins (Ph.Eur.), microbial quality (Ph.Eur.), and particulate matter. Limits set up for the impurities and the residual solvents are acceptable and in line with ICH guidelines.

Analytical methods have been appropriately described and non-compendial analytical methods such as methods for identity, assay, determination of related substances and residual solvents have been satisfactorily validated in accordance with ICH requirements. The proposed analytical methods are considered adequate for their intended use.

Batch analysis results have been provided for nine production-scale batches of olanzapine pamoate monohydrate. Additionally, nine pilot-scale batches were also tested. All results met the proposed specifications.

Container closure: The active substance is kept in a container made of stainless steel and a bottom valve with polytetrafluoroethylene (PTFE) diaphragm. Certificates of Analysis have been provided for the packaging materials. The container closure system is considered adequate and is supported by stability data.

- Stability

Stability studies have been conducted on three commercial batches under ICH conditions (up to 24 months at 25°C/65% RH and 6 months at 40°C/75% RH). The following parameters were studied: appearance, crystal form, assay, related substances, water content, particle size, bacterial endotoxins, and microbial quality. The analytical methods are considered as adequate.

In addition, stress testing studies were performed to understand the intrinsic stability of the active substance under various conditions (heat, light, humidity, and different pH conditions). These studies showed that olanzapine is sensitive and degradation was observed under acid and basic conditions, light exposure, and oxidative conditions.

The active substance was shown to be stable when kept in the commercial container under long-term and accelerated conditions. No significant trend was observed for any of the tested parameters. All physico-chemical and pharmaceutical parameters remained within the authorised limits. Stability data support the proposed re-test period.when stored in the commercial stainless steel container closure system.

Medicinal Product

The primary packaging consists of: a vial containing olanzapine pamoate salt (no excipient), as yellow powder (equivalent to 210 mg, 300 mg, or 405 mg of olanzapine base), and a vial of single-use sterile, viscous liquid.

Immediately prior to administration, the aqueous vehicle is combined with the olanzapine powder to form a suspension for intramuscular injection (olanzapine pamoate depot). The olanzapine pamoate suspension has a target concentration of 150 mg/ml olanzapine base for all dosage strengths.

- Pharmaceutical Development

Olanzapine pamoate powder:
The pharmaceutical development of the powder has been appropriately detailed and the choice of the olanzapine pamoate salt was justified based on its low aqueous solubility for drug release, low hygroscopicity, chemical and physical stability a well as from manufacturing and terminal sterilization point of view.

No excipient was used with the active substance powder.

The formulation development aimed to be a parenteral suspension product that would optimize the suspension concentration and minimize the injection volume for the three strengths, namely 210 mg, 300 mg, and 405 mg. The volume of injection was determined to be between 0.5 ml to 3 ml, which is relevant to intramuscular injection. The viscosity of suspension was taken into account to allow the suspension to be easily drawn into a syringe and injected.
To achieve the same concentration, a different amount of vehicle was used to suspend each of the three doses. The suspension and dosing strategy has been confirmed in clinical studies.

Overage has been applied and justified: an excess of the active substance was included to ensure the targeted dose to be administered.

The manufacturing development has been sufficiently detailed and a real-time control approach was selected. The proposed technology provides real-time dose control of the commercial filling process. A Failure Mode Effects Analysis (FMEA) was performed on the technology application in order to minimize or control manufacturing process factors that could affect the drug product filling process controls. The FMEA analysis provided commercial filling line improvements

Also, electron beam terminal sterilisation was selected since the container closure system was unstable under dry heat processing conditions and moist heat sterilization was inappropriate for a dry powder formulation. Furthermore, in relation to the microbiological attributes, the sterilization method is justified for the proposed pharmaceutical form.

In summary, it has been confirmed that the composition of manufactured drug product batches for toxicology and clinical studies has remained the same for all dosages of the present medicinal product.

In conclusion, the manufacturing process development was adequately described and the proposed final commercial process involving crystallisation, dry-powder filling and terminal sterilisation leads to a finished product of consistent quality.

Vehicle
The formulation development of the vehicle was aimed to a stable solution that would allow the drug product to be easily suspended and injected.

All excipients comply with their respective Ph.Eur. monographs. The following excipients were used: carboxymethylcellulose sodium (carmellose sodium), mannitol, polysorbate 80, water for injection, sodium hydroxide solution 10%, hydrochloric acid solution 10%.

Development studies have demonstrated that all manufacturing processes of the drug product formulation have provided comparable chemical, physical, and microbiological control during manufacturing and throughout the drug product shelf life. Batches used in the clinical studies and for the stability studies were obtained by the final manufacturing process

An overfill has been retained for the vehicle to ensure withdrawal of the correct amount of vehicle.

The manufacturing process development has been adequately detailed In addition, the choice of sterilization method (terminal sterilisation under moist heat conditions) is justified for the present vehicle and parenteral injection.

The choice of containers for the powder and the vehicle (5 ml, type I glass vials closed by butyl rubber stoppers) has been discussed. The glass vial complies with Ph.Eur. monograph 3.2.1 Glass Containers for Pharmaceutical Use and the stopper complies with Ph.Eur. monograph 3.2.9, Rubber Closures for Containers for Aqueous Parenteral Preparations for Powders and Freeze-Dried Powders.

- Adventitious Agents

No excipients of animal or human origin have been used in the manufacture of the vehicle.

- Manufacture of the Product

Manufacture of the powder:
The manufacturing of the powder has been satisfactorily described and consists of the following main steps: (1) Preparation of container closure components (cleaning, washing, sanitizing and depyrogenation processes), (2) Filling of olanzapine pamoate (automated filler), (3) Sealing, (4) Exterior vial rinsing, (5) Packing for terminal sterilization, (6) Terminal sterilization, and (7) Secondary packaging and labelling. Appropriate in-process controls have been applied.

Manufacture of the vehicle
The manufacturing of the vehicle has been satisfactorily described and consists of the following main steps:(1) dissolve mannitol in Water for Injection, (2) addition of sodium carmellose,(3)and (4) dissolution and homogeneisation,(5) dissolution of polysorbate 80 in WFI, (6) mixing, (7) pH adjustment, (8) filtration and aseptic filtration 0.22 µm, (9) filling, (10) sealing, (11) terminal sterilisation and control. Appropriate in-process controls have been applied.

Process Validation and/or Evaluation

Process validation has been performed on three production-scale batches of powder (one batch for each strength, manufactured according to the commercial process. All batches were conform to the specifications at all tested time points and sampling positions. Prior to the release of the drug product to the marketplace, the manufacturing process will be validated which is acceptable for a terminal sterilisation process.

The process validation of the proposed terminal sterilization for the powder has been described in detail. Sterility for all manufacturing batches at release has been demonstrated. In addition, the drug product has been shown to remain sterile through 24 months. Furthermore, based on the results, no degradation products are found as a result of irradiation and the total degradation products do not increase with repeat doses of radiation. Therefore the drug product terminally sterilized using electron beam irradiation is proven to be stable during storage.

The process validation of the terminal sterilization (for the vehicle) has been satisfactorily detailed.

- Product Specification

Release and end of shelf-life specifications for the powder include the following parameters: appearance (visual), uniformity of dosage units (Ph.Eur.), identification (IR), assay of the active substance (HPLC), related substances (HPLC), dissolution (Ph.Eur.), injectability (force), particulate matter (Ph.Eur.), sterility (Ph.Eur.), bacterial endotoxins (Ph.Eur.).

Release and end of shelf-life specifications for the vehicle include the following parameters: appearance (visual), colour (Ph.Eur.), clarity (Ph.Eur.), identification (IR and HPLC), particulate matter (Ph.Eur.), viscosity, sterility (Ph.Eur.), bacterial endotoxins (Ph.Eur.)
Analytical methods have been described and adequately validated in accordance with ICH requirements.

Powder: Batch results are provided for production-scale batches of each of the dosage strengths manufactured at the proposed commercial site and results comply with the release specification

Vehicle: Batch results are provided for five production-scale batches. All results were in compliance with the release specification.

- Stability of the Product

Stability of the powder
Stability studies have been carried out on 10 pilot batches kept in the commercial packaging under ICH conditions (results available until 12 months at 30°C/65%RH and 6 months at 40°C/75%RH).
The physical and chemical properties of the drug product demonstrated in the solid state stability studies afford similar drug product stability when suspended in the vehicle. The data provided indicate that minimal stability changes are expected as a drug product in the suspension state intended for immediate use for up to 24 hours. The observed physical changes (suspension state particle size, injection efficiency) in the suspension are minimal and seem to have no impact on clinical performance. In summary, stability of the drug product has been studied in the solid state (powder) and in the suspension state and the stability protocol agreed.

Parameters studied included physical appearance (description), assay, degradation product content, *in vitro* dissolution, injectability, bacterial endotoxins, particulate matter and sterility.
Supporting stability studies on twelve batches (obtained by an earlier development process for clinical trials) are also available after 24 months at 30°C/65%RH and up to 36 months at 25°C/60%RH.
Stability results showed that no significant degradation trend could be observed and the results remain within the specification. Results support the shelf-life and storage conditions as defined in the SPC for the powder and the final suspension.

Stability of the drug product vehicle (solvent)

Separate stability studies have been conducted on the vehicle on three commercial batches kept in the commercial packaging under ICH conditions (results available until 12 months at 30°C/65%RH and 6 months at 40°C/75%RH).
Parameters studied included physical appearance, colour and clarity, pH, viscosity, particulate matter, bacterial endotoxin, and sterility.
No significant change could be observed during the stability studies.
Results support the shelf-life and storage conditions as defined in the SPC for the vehicle.

Photostability studies conducted under ICH conditions have demonstrated that the drug product is stable in the solid and suspension states when kept in the commercial packaging.

Discussion on chemical and pharmaceutical aspects
Information on development, manufacture and control of the active substance olanzapine pamoate and the drug product olanzapine depot formulation has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of the important product quality characteristics and in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3 Non-clinical aspects

Introduction

As the pharmacology of olanzapine is not expected to be altered by the method of administration, the pharmacology dossier submitted to support the MAA of Zypadhera is mainly based on the findings reported in the dossier for oral olanzapine. Some secondary pharmacodynamics studies were conducted to investigate the effect of olanzapine treatment on body weight and development of diabetes. The set of safety pharmacology studies was completed to include data relative to the ability of olanzapine to block cardiac ion channels.

Pharmacology

- Primary pharmacodynamics

The applicant refers to the primary pharmacodynamics findings reported in the MAA for oral olanzapine. It is indicated that the receptor binding profile of olanzapine has been expanded to include additional receptor subtypes.

Olanzapine is an atypical antipsychotic with a broad binding and pharmacological profile. *In vitro*, olanzapine showed medium-to-high affinity (Ki <100 nM) for dopamine D_1, D_2, D_3, $D_{4.2}$, D_5, serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, α_1-adrenergic, histamine H_1, and 5 muscarinic receptor subtypes. Olanzapine had lower affinity for α_2-adrenergic receptors and relatively low affinity for 5-HT1 subtypes, $GABA_A$, β-adrenergic, and benzodiazepine binding sites. Overall, the binding profile of olanzapine is very similar to that produced by clozapine, although the affinity of olanzapine is somewhat higher at dopamine receptors and lower at α_2-adrenergic receptors.

Additional *in vitro* and *in vivo* biochemical pharmacology studies with olanzapine confirmed potent 5-$HT_{2A/2C}$, dopamine D_1, D_2, and muscarinic antagonist activity. Of particular interest were studies demonstrating that olanzapine antagonized quipazine-induced (5-HT receptor agonist) and pergolide-induced (dopamine D_2 agonist) increases in corticosterone in rats. These results show that olanzapine has more potent activity at 5-HT receptors than at dopamine D2 receptors *in vivo.*

In electrophysiological tests, when rats were dosed orally with olanzapine for 21 days, there was a decrease in the firing rate of mesolimbic dopamine neurons (A10 cells), whereas the activity of the neurons of the striatal system (A9 cells) was either unaffected or increased (see figure 2). Thus, olanzapine preferentially modified the brain mesolimbic dopaminergic system suggesting that this compound could be less likely to produce extrapyramidal side effects.

In vivo, olanzapine blocked conditioned avoidance in rats at lower oral doses than those which produced catalepsy, increased punished responding in conflict models, and substituted for clozapine in a drug discrimination assay.

- Secondary pharmacodynamics

Literature reports suggest that long term use of atypical antipsychotic drugs is involved in the risk for development of adverse metabolic effects including glucose intolerance/diabetes mellitus, hyperlipidemia, hyperleptinemia, and weight gain (Melkersson et al, 2004, Newcomer 2007). The underlying mechanisms are not yet fully understood but some authors showed that atypical antipsychotics directly modulate insulin action and metabolic processes in insulin target tissues including insulin-stimulated glucose transport in adipocytes and skeletal muscle cells (Vestri et al. 2007, Engl et al. 2005).

From 2001 to 2007, the applicant studied the effect of olanzapine treatment on body weight and development of diabetes.

Subcutaneous administration of olanzapine to female rats with osmotic mini-pumps for 10 to 19 days produced a significant compound-associated increase in weight gain over vehicle-treated animals (studies CNS590 and CNS371). However, male rats treated the same way, did not show increases in weight gain.

In another study (no. PsD32), oral administration of olanzapine to female rats (0.2 mg/kg, 31 days) also produced a significant compound-associated increase in weight gain which was due to a specific increase in fat mass as opposed to fat-free mass. Concomitant oral treatment of rats with olanzapine and 2.5 mg/kg cannabinoid 1 (CB1) receptor antagonist for 12 days caused a reduction in fat mass, but did not modify body weight or food intake.

Another study (no. PsD33) determined if a CB1 receptor antagonist could prevent treatment-emergent weight gain associated with olanzapine. The CB1 receptor antagonist, when dosed orally together with olanzapine, was able to attenuate olanzapine treatment-emergent weight gain although this effect was not significantly different compared to olanzapine treatment alone. Similarly, concomitant oral treatment of rats with olanzapine and a pan-opiate antagonist for 15 days (following 15 days of oral treatment with olanzapine alone) reversed the body fat gain to vehicle treated levels (study PsD36).

To determine if olanzapine treatment would potentiate development of diabetes, 7 week old male Zucker diabetic fatty rats were treated with olanzapine before these animals became diabetic. Olanzapine did not accelerate development of hyperglycemia and hypoinsulinemia in this model (study CNS378).

Two final studies were done to examine potential causes of the olanzapine treatment emergent weight gain. The first used female Sprague Dawley rats treated with subcutaneous olanzapine in a pamoate-sustained delivery system, and plasma ghrelin levels were examined. These results demonstrated that olanzapine-induced increases in food consumption and body weight are not secondary to increased plasma ghrelin levels (study no. ALW01). The final study was done because it has been demonstrated that antipsychotic drugs which produce weight gain increase Fos expression in a high percentage of orexin-containing neurons of the lateral hypothalamus. Olanzapine produced a significant increase in the percentage of orexin cells that also expressed Fos relative to vehicle (study CNS562).

- Safety pharmacology programme

In earlier studies safety pharmacology of olanzapine has been well characterized. The main findings regarding the cardiovascular system showed that olanzapine, as other antipsychotic agents, dose-dependently blocks the cloned equivalent of the delayed rectifier potassium current I_{Kr} with an IC50 amounting to 0.231 µM. Other ionic currents were blocked at higher concentrations. The risk of QTc prolongation is adequately reported in SPC section 4.4. In addition, hypotension was observed in

anaesthetized rats and dogs administered an IV bolus (0.1 mg/kg), but not in conscious rats treated orally at 10 mg/kg. The risk of hypotension is addressed in various sections of the SmPC.
Other studies conducted by the oral route were already evaluated; among other CNS effects reported in mice, some findings suggest a proconvulsive activity of olanzapine.

- Pharmacodynamic drug interactions

No specific pharmacodynamic studies to evaluate drug interactions have been conducted. This is acceptable as the results of clinical drug interaction studies performed with oral and RAIM olanzapine are a sufficient reliable characterization of what to expect with OP Depot in similar situations.

Pharmacokinetics

Olanzapine has been extensively evaluated as an oral agent and as a rapid acting IM agent. The absorption and exposure of olanzapine and/or pamoic acid following administration of OP Depot in rats, rabbits and dogs were conducted in support of current application. The primary evaluation of olanzapine pamoate has focused on the absorption of the salt form, as other aspects of the disposition (distribution, metabolism, excretion, etc) would be expected to remain unchanged once the compound is absorbed.

Absorption

In rat, dog, and rabbit, OP Depot produced initial peak plasma concentrations of olanzapine and pamoate followed by a gradual decline in concentrations for up to 28 days postdose. Plasma concentrations of olanzapine following the administration of OP Depot increased with increasing dose. Plasma concentrations of pamoic acid were greater following the administration of pamoic acid alone compared to the administration of OP Depot. The plasma profiles of pamoic acid following administration of OP Depot were qualitatively similar to those obtained following administration of pamoic acid alone. Studies compared the maximum exposure to olanzapine in rats and dogs respectively, following administration of oral olanzapine (daily) or OP Depot either once/4 weeks in rats or once/2 weeks in dogs. During an 8-week period, male rats given oral olanzapine were exposed to 9.1 times more olanzapine and female rats were exposed to 13.4 times more olanzapine than rats given 3 IM injections of the highest feasible dose of OP Depot. Additionally, male dogs in the oral study following 6 months of treatment were exposed to 9.9 times more olanzapine and female dogs were exposed to 6.4 times more olanzapine than the dogs in the 6-month olanzapine pamoate monohydrate study following 13 injections of IM OP Depot.
Thus, the relative lack of systemic toxicity in the nonclinical toxicology studies with olanzapine pamoate monohydrate is to be expected based on lower levels of exposure.
Comparison of olanzapine plasma exposure in rat and dog following administration of oral olanzapine versus intramuscular administration of OP Depot showed slower absorption of olanzapine (a single dose of OP Depot) in dogs (Tmax approximately 3 to 6 days) compared with absorption in rats and rabbits (Tmax under 24 hr). The Applicant was invited by the CHMP to comment the reasons for this interspecies variation in absorption rate. The argumentation was that this variability is likely due to multiple physiological and physical factors including differences in the placement of the injection, the size of the muscle mass being injected (larger in dog than in rat), the blood flow to the region of injection, and the different species themselves, all of which could contribute to variable absorption from the site. Regardless of this variability, the overall pharmacokinetic pattern is however predictable in all species, with absorption to Tmax in a comparatively short period of time (hours or days), followed by sustained exposure over weeks, which is expected of an IM depot administration. The CHMP accepted the reasoning of the applicant.

Distribution

The distribution of orally administered olanzapine in laboratory animals has been well characterized.
Olanzapine is widely distributed throughout the body, with a Tmax of 2 hours for the majority of tissues in the single-dose study and is cleared relatively quickly; by 96 hours after dosing, most tissues had non detectable levels of radioactivity. Olanzapine half-lives ranged from approximately 3 to 9

hours. Olanzapine was shown to have a fairly high degree of binding to plasma proteins in each of the species examined. The mean plasma protein binding of 14C-olanzapine ranged from 58% to 63% in the cynomolgus monkey, 72% to 77% in the dog, 71% to 81% in the mouse, 80% to 85% in the rhesus monkey, and 84% to 91% in the rat. Pregnant rats given oral doses of 14C-olanzapine on Gestation Day 12 or 18 had high levels of radioactivity in most maternal tissues, but very low levels (≤0.04% of the dose) were detected in fetal tissues.

No distribution studies were conducted with olanzapine pamoate monohydrate as the distribution of olanzapine following i.m. administration would be substantially identical to that observed for oral olanzapine following absorption.

Standard distribution, protein binding, or placental transfer studies for pamoic acid were not conducted, as these studies were not needed to support toxicology or clinical endpoints. However, a 14C-pamoic acid distribution study was conducted in mice to support genetic toxicology studies. This study demonstrated pamoic acid distribution to bone marrow.

Metabolism

Metabolism of oral olanzapine has been thoroughly characterised in various animal species and in human. Each species produced a different major urinary metabolite; in human it was the 10-N glucuronide. Metabolites of olanzapine were detected also in the plasma of mice, rats and dogs, but the single largest entity was olanzapine itself. In humans, olanzapine, N-10-glucuronide, N-desmethyl-olanzapine, the 4'-N-oxide analogue, and the 2-hydroxymethylmetabolite were found. No 7-hydroxy-olanzapine was detected in the plasma of humans receiving an oral dose of olanzapine.
In vitro studies have shown that the formation of various metabolites is linked to cytochrome P450 isoform CYP2D6, CYP1A2, and the flavin-containing enzyme known as FMO3.
A non-clinical evaluation of the metabolism of olanzapine following administration of OP Depot was not conducted, but the metabolic profile was assessed in humans. Overall, the olanzapine-related metabolic profiles for human urine and plasma after administration of oral olanzapine and OP Depot were similar.

The metabolism of pamoic acid was assessed both *in vivo* and *in vitro*, and the findings showed that there is no metabolism of pamoic acid in rats.

Excretion

The excretion of 14C-labeled olanzapine had been previously determined in mice, rats, dogs, monkeys, and humans and the excretion of olanzapine into the milk of lactating rats was also previously evaluated. Further the excretion of 14C-labeled olanzapine was evaluated in dogs following both IM and intravenous administration. Mice, rats, and dogs eliminated the majority of the radioactivity associated with a single oral dose of 14C-olanzapine into the feces. On the contrary, monkeys (and humans) excreted most of the radioactivity from an oral dose via the kidneys. Following a single IM administration of 14C-olanzapine, dogs excreted 46.1% and 42.2% of the radioactivity in the urine and feces, respectively. The majority of the radioactivity in the feces of rats was due to extensive biliary excretion. Rats also demonstrated a considerable first-pass effect, as shown by portal-versus-systemic plasma measurements, as well as a noteworthy enterohepatic recirculation of biliary-excreted metabolites.

In a study evaluating the plasma pharmacokinetics of pamoic acid, after a single IM injection of 14C-pamoic acid to male rats, residual radioactivity in urine, faeces, cage wash, and carcass was determined by liquid scintillation counting (study 007R02). The mean total recovery of radioactivity was 98.2 % of the administered dose after 168 hours with 97.8 % of the dose recovered after 72 hours. The majority of radioactivity was recovered in faeces, 97.5 % of the dose after 72 hours. Urine, cage wash, and carcass accounted for only approximately 0.3%, 0.11% and 0.11%, respectively, of the administered radioactivity.

Toxicology

The toxicology development program for olanzapine pamoate monohydrate is based on studies previously conducted with olanzapine. The applicant performed bridging studies in rats (3 months) and dogs (6 months) by the intramuscular route with OP Depot, as no qualitative differences in metabolites between oral and depot forms is expected in humans. In addition, genotoxicity studies were performed with pamoic acid, as well as a carcinogenicity study in rats and reproductive toxicity studies in rats and rabbits.

- Single dose toxicity

Single dose toxicity studies were performed with OP Depot in rats and dogs at doses up to 10 mg and 20 mg/kg. No sign of systemic toxicity was noted in both species; the findings were limited to injection site reactions.
In rats, a chronic inflammation was observed at the injection site, and was consistent with a foreign body reaction. The severity of the lesion decreased post-dosing but remained evident 42 days after the injection. Similar findings were observed in pamoic acid-treated rats, but the inflammation was of lesser duration.
In dogs, chronic inflammation with fibrosis was reported at the injection site. Both incidence and severity of the lesion did not depend on the dose level (5, 10, 20 mg/kg).

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicity studies performed with OP Depot were conducted in rats (0, 20, 50, 100 mg/kg/4 weeks, plus a group dosed with pamoic acid at 125 mg/kg/4 weeks, a dose corresponding to that given in the 100 mg/kg/4 weeks OP Depot group, three month duration) and in dogs (0, 5, 10, 20 mg/kg/2 weeks, plus a group dosed with pamoic acid at 25 mg/kg/2 weeks, a dose corresponding to that given in the 20 mg/kg/2 weeks OP Depot group, six month duration).

In rats, a decrease in body weight was noted at 50 and 100 mg/kg (-26% to -39% at 100 mg/kg). This finding was already reported in studies with oral olanzapine. Injection site reactions were also observed in all treated groups, and consisted of dose-dependent granulomatous inflammation due to the presence of olanzapine and foreign bodies. The atrophy of myocytes, the fibroplasia and increased collagen deposition were graded minimal in severity. From this study, the NOAEL for systemic effects is 20 mg/kg/4 weeks (decreased body weight). No NOAEL could be determined for injection site reactions.

In dogs, no systemic effect was noted. At the injection site, redness, swelling and ulceration were reported. At the histopathological level, it corresponded to chronic inflammation. These lesions were dose-dependent and generally resolved within 2 weeks. From this study, the NOAEL for systemic effects is 20 mg/kg/2 weeks. No NOAEL could be determined for injection site reactions.

AUC-based exposure multiples ranged from 0.2 to 0.5 in rats, and from 0.12 to 0.6 in dogs at the NOAEL for systemic toxicity. At the same dose levels, Cmax-based exposure multiples range from 1.8 to 2.7 in rats, and from 0.6 to 1.1 in dogs. As indicated by the applicant, the high-dose levels used in these studies were limited by the suspension volume that could be humanely injected and the maximum suspendable concentration.

- Genotoxicity

Carcinogenic potential of olanzapine has been evaluated previously for the oral form development, and it showed not to be of concern for humans.

Pamoic acid did not show any genotoxic activity in the Ames test, in the mouse lymphoma assay, in a chromosomal aberration assay in human lymphocytes, and in an *in vivo* micronucleus test in mice. The latter test was conducted by IM route, at doses up to 586.2 mg/kg in males, and 684.2 mg/kg in

females. A pharmacokinetic study adequately showed that pamoic acid distributed to the bone marrow.

A positive result was obtained in an *in vitro* chromosomal aberration assay conducted with CHO cells. The incidence of cells with aberrations is increased at 1750 µg/mL, and amounted to 3.5% excluding gaps and 4.5% including gaps (non significant in the latter case). The incidence of cells with diplochromosomes reached 13.5%. In a second experiment, the only finding was an increase of the percentage of cells with diplochromosomes (10%, vs. 0% in control group) at 1750 µg/mL. In another study with extended cell exposure, positive results are obtained from 1250 µg/mL. At this concentration level, the percentage of cells with aberrations amounted to 4% excluding gaps (8.5% at 1400 µg/mL). With metabolic activation, positive results are obtained from 900 µg/mL (15.5% cells with aberrations, excluding gaps). Pamoic acid is not metabolized in rats.

Taking account the negative results in 3 other genetic toxicology assays and in the 2-year rat bioassay with olanzapine pamoate monohydrated and pamoic acid, it was concluded that the compound does not constitute a genotoxic or carcinogenic risk to patients.

- Carcinogenicity

A study in mice could not be performed for technical reasons (insufficient muscle mass, needle required was too large).

In rats, no effect of treatment on survival was observed. There were no increases in tumour incidence in treated versus vehicle-control animals. Dose-related increases in injection site irritation were observed although the effect was no worse than what was observed in the 3-month study (that is, there was no progression of inflammation). Injection site irritation was generally mild and consistent with what would be expected for a normal inflammatory reaction to a depot injection.

- Reproduction Toxicity

Two embryo-fetal toxicity studies were conducted with OP Depot and pamoic acid. The effects observed were limited to injection site reactions in dams. No embryotoxic or teratogenic effect was reported in either rat or rabbit. In both species, the NOELs for maternal systemic toxicity and embryo-fetal development amounted to 75 mg/kg. In a pre/postnatal toxicity study performed in rats, a lack of habituation to the startle response in the F1 males with a reduced performance on memory trials in the Biel Maze at 75 mg/kg were observed. As indicated by the applicant, these findings were also found in studies with oral olanzapine. The NOAEL for maternal systemic toxicity reached amounted to 75 mg/kg, and the NOAEL for F1 development was 25 mg/kg. As mentioned previously, the high-dose levels used in these studies were limited by the suspension volume that could be humanely injected and the maximum suspendable concentration.

- Local tolerance

Separate studies on local tolerance have not been performed. However, injection sites of animals included in single and repeat dose toxicity studies were both clinically and histopathologically examined. The primary toxicity of OP Depot in laboratory animals was injection site irritation.

- Other toxicity studies

No other toxicity studies were performed by the applicant for OP Depot.

The EPAR for Zyprexa mentions that immunotoxicity studies were carried out in a small number of mice at dose of 3 to 45 mg/kg. Lymphopenia and neutropenia were seen at high doses. Overall, immune function was relatively unaltered although an increase in B lymphocyte count and decrease in NK activity in the spleen was shown. It is also indicated that no dependency potential was found with olanzapine in rats and monkeys at doses of 0.05 to 32 mg/kg and 0.06 to 8 mg/kg, respectively, as shown by evaluation of self-administration and physical dependence on olanzapine.

In addition, an antigenicity study was conducted in guinea pigs. Active systemic anaphylaxis or passive cutaneous anaphylaxis were not elicited, and olanzapine was judged to have neither antigenic or hapten properties.

No dependency studies were conducted with OP Depot. In studies conducted with oral olanzapine no evidence of olanzapine drug dependence was demonstrated in rats or rhesus monkeys.

Ecotoxicity/environmental risk assessment

Log Kow and Koc values were determined by the applicant. They show that olanzapine has a low potential for bioaccumulation and is weakly adsorbed in the sediment. In a 28-day biodegradation assay in sludge, the half-life of olanzapine was short (DT50 = 7.4 days), whereas it underwent a slow hydrolysis in surface water (> 50 days).

It can be concluded that olanzapine has no bioaccumulation potential. In addition, it is rapidly degraded in sewage treatment plants (half-life = 7.4 days) and also in aquatic sediments either in aerobic or anaerobic conditions (DT90 = 2.6 days, and 14.6 – 17.2 days, respectively). Ecotoxicity studies were conducted with various aquatic species (microorganisms, algae, daphnids, fishes). PEC/PNEC ratios calculated for surface water, groundwater, and sewage treatment plant do not exceed the value of 1.

Therefore, it is considered that Zypadhera does not present a significant risk to the environment.

Discussion on the non-clinical aspects

Olanzapine has been extensively evaluated as an oral agent and as a rapid acting IM agent. The current application concerns a sustained release salt form of olanzapine with pamoic acid, creating an IM injection that allows long-term exposure to olanzapine over a period of weeks. The primary evaluation of olanzapine pamoate has focused on the absorption of the salt form, as other aspects of the disposition (distribution, metabolism, excretion, etc) would be expected to remain unchanged once the compound is absorbed.

Comparison of olanzapine plasma exposure in rat and dog following administration of oral olanzapine versus intramuscular administration of OP Depot showed slower absorption of olanzapine (a single dose of OP Depot) in dogs (Tmax approximately 3 to 6 days) compared with absorption in rats and rabbits (Tmax under 24 hr). The Applicant was invited by the CHMP to comment the reasons for this interspecies variation in absorption rate. The argumentation was that this variability is likely due to multiple physiological and physical factors including differences in the placement of the injection, the size of the muscle mass being injected (larger in dog than in rat), the blood flow to the region of injection, and the different species themselves, all of which could contribute to variable absorption from the site. Regardless of this variability, the overall pharmacokinetic pattern is however predictable in all species, with absorption to Tmax in a comparatively short period of time (hours or days), followed by sustained exposure over weeks, which is expected of an IM depot administration. The CHMP accepted the reasoning of the applicant.

Pamoic acid is well absorbed in mice and rats following IM administration of pamoic acid alone or with olanzapine in the OP Depot formulation. Pamoic acid is rapidly excreted in rats via the feces. Plasma exposures and pharmacokinetic profiles of pamoic acid and radioactivity derived from 14C-pamoic acid were similar in rats, suggesting that pamoic acid is no metabolized. Thus pamoic acid, derived from the pamoate salt, is absorbed and rapidly excreted unchanged in non clinical species.

The salient features of olanzapine oral toxicity were sedation and systemic toxicity secondary to elevated prolactin concentrations. Leukopenias were observed in all 3 nonclinical models: lymphopenia predominantly occurred in mice and an idiosyncratic, but dose-related incidence of neutropenia occurred in dogs. Rats given 16 mg/kg/day had decreased lymphocyte and neutrophil counts and atrophy of bone marrow consistent with the marked reduction in body weight gain.

Notwithstanding these earlier observations for oral olanzapine in nonclinical models, olanzapine has been well tolerated in patients and hematologically related observations have been infrequent

Inflammation at the injection site was extensive in dogs treated with OP Depot. Dogs developed acute inflammatory responses, and the duration of the responses appeared to be dose related. Rats given OP Depot intramuscularly appeared to have less severe reactions than dogs.

No increases in fetal toxicity or malformation were observed in the embryo-fetal studies in rats or rabbits with OP Depot. Minor changes in behavioral development of offspring were observed at the highest dose employed in the perinatal/postnatal development study.

None of the nonclinical studies conducted with olanzapine pamoate monohydrate identified any new toxicity due to systemic exposure to olanzapine. The high dose used in both rat and dog studies were limited by the suspension volume that could be humanely injected and the maximum suspendable concentration. Injection site reactions occurred in both rats and dogs precluding identification of no-effect doses; however, these laboratory animals appear to react more readily than humans studied to date. As addressed above, systemic concentrations in these studies were generally less than that seen at effect levels in the oral studies; thus, the lack of systemic toxicity is not surprising.

The compound does not constitute a genotoxic or carcinogenic risk to patients.

2.4 Clinical aspects

Introduction

Olanzapine is a well-known medicinal product, already approved for oral and immediate-release intra-muscular use. The applicant has developed a new sustained-release depot for IM route using a practically insoluble salt (pamoate monohydrate).
The depot formulations are to be administrated once every two or four weeks and aimed to provide a consistent exposure to olanzapine comparable to that observed with the once daily oral administration of Olanzapine.
Three strengths are claimed: 210- 300 and 405 mg (equivalent olanzapine free base). When reconstituted adequately with solvent, all these strengths lead to the formation of a high solids contents aqueous suspension exhibiting the same potency (150 mg/ ml olanzapine free-base).

The phase III program of Zypadhera submitted by the Applicant is based on two main studies, HGJZ (8-week randomized placebo controlled superiority study) and HGKA 24-week randomized active controlled versus oral olanzapine non inferiority study. No formal dose-finding studies were performed and doses were selected according to pharmacokinetic data. A long-term, open label study (HGKB) having safety, effectiveness and PK as objective was ongoing at the time of the opinion.

The initially sought indication was

Treatment of schizophrenia. ZYPADHERA is effective in the treatment of patients who have previously been exposed to oral olanzapine.
Maintenance treatment of schizophrenia. ZYPADHERA is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response to oral olanzapine.

However, further to discussion with the CHMP (see Discussion on Efficacy), the applicant agreed to change the indication to

Maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

Taking into account the nature of the application under consideration, the applicant has conducted PK studies in order to elucidate the PK behaviour of Zypadhera and to make comparison with the already approved and well characterised oral and RAIM (Rapid Acting Intra Muscular) routes.
The clinical pharmacokinetics development program conducted by the applicant has taken into account the ethical constraints imposed by the pharmacological profile of olanzapine. Consequently only a pilot phase I study has been conducted in healthy volunteers. All PK pivotal studies have been conducted in patients.

A total of 18 healthy volunteers and 412 patients were enrolled in five formal PK studies, LOBS, LOAZ, LOBE, LOBO, and LOBQ that are described in the table below.

Study Identifier (F1D); Status; Report Type	**Primary Objective and Endpoint(s) Secondary Objective(s)**	**Enrollment Start Status End**	**Design; Control Type**	**Test and Control Drug(s) Dose, Route, and Regimen**	**No. HS or P Enrolled (M/F) Median Age (Range) years No. completed**	**Diagnosis; Inclusion Criteria**	**Treatment Duration**
EW-LOBS; Complete; Full CSR	To assess the acceptability of sustained-release product performance bioavailability characteristics of 4 OP Depot lots relative to bioavailability parameters for oral olanzapine Further evaluations included assessment of the in vivo release profile and sustained-release product performance bioavailability characteristics of 4 OP Depot lots relative to bioavailability parameters for RAIM olanzapine; also safety and tolerability	Sept 04 Completed Mar 06	Fixed-sequence, open-label	Study Period I: OLZ tablets, 5 to 20 mg, PO, every day Study Period II: OP Depot, 405 mg, IM injection, administered once Study Period III: RAIM OLZ, 5 mg, IM, administered once	Study Period II[a] 134 P (95/39) 38 (18–67) 126 completed	Schizophrenia or schizoaffective disorder as defined by DSM-IV; patients must have been stable for at least 4 weeks prior to Visit 1 and must have tolerated oral olanzapine well in the past.	Study Period I: 14 days, PK measurements for 24 hours after Day 14 dose Study Period II: one administration, PK measurements for 26 days Study Period III: one administration, PK measurements for 5 days

[a] 165 patients entered Study Period I. Of the 134 patients who entered Study Period II, 126 patients entered Study Period III.

Study Identifier (F1D); Status; Report Type	**Primary Objective and Endpoint(s) Secondary Objective(s)**	**Enrollment Start Status End**	**Design; Control Type**	**Test and Control Drug(s) Dose, Route, and Regimen**	**No. HS or P Enrolled (M/F) Median Age (Range) years No. completed**	**Diagnosis; Inclusion Criteria**	**Treatment Duration**
EW-LOAZ; Complete; Full CSR	Safety and tolerance as measured by AEs, laboratory analysis, vital signs, ECGs, alertness, and injection pain score Evaluation of absorption characteristics and evaluation of PK profile	Jan 00 Completed Aug 00	Open-label	OP Depot; 10, 15, 20, or 40 mg; IM; administered once OLZ, 10 mg, PO, administered once	18 HS (18/0) 34 (20–48) 18 completed	Healthy male subjects, aged 18 to 55.	Each subject received a single dose of oral olanzapine on one occasion, then a single dose of OP Depot (10, 15, 20, or 40 mg) on another occasion. There was a period of at least 7 days between the administration of the oral and depot dose.

Study Identifier (F1D); Status; Report Type	Primary Objective and Endpoint(s) Secondary Objective(s)	Enrollment Start Status End	Design; Control Type	Test and Control Drug(s) Dose, Route, and Regimen	No. HS or P Enrolled (M/F) Median Age (Range) years No. completed	Diagnosis; Inclusion Criteria	Treatment Duration
EW-LOBE; Complete; Full CSR	Safety and tolerance as measured by vital signs, clinical laboratory tests, and ECGs. PK, dosing, evaluation of maintenance of psychiatric control	Aug 00 Completed Apr 03	Open-label	SDG: OP Depot, 50 to 450 mg, IM, administered once MDG: OP Depot, 100 to 405 mg, IM, administered every 2, 3, or 4 weeks No control drug	SDG: 34 P (27/7) 39 (20–55) 30 completed MDG: (6 months) 223 P (158/65) [a](18–65) 153 completed MDG: (3 months) 25 P (22/3) [a](21–63) 23 completed	Schizophrenia	SDG: 28 days MDG: 3 or 6 months

Study Identifier (F1D); Status; Report Type	Primary Objective and Endpoint(s) Secondary Objective(s)	Enrollment Start Status End	Design; Control Type	Test and Control Drug(s) Dose, Route, and Regimen	No. HS or P Enrolled (M/F) Median Age (Range) years No. completed	Diagnosis; Inclusion Criteria	Treatment Duration
EW-LOBO; Complete; Full CSR	PK profiling measured by plasma concentrations of OLZ and pamoic acid and metabolic profiling measured by urine and fecal samples Determination of systemic exposure to pamoic acid, further evaluate the metabolic profile	Jun 02 Completed May 03	Open-label	OP Depot, 300 mg, IM, administered every 14 days until 4 injections have been given	9 P (8/1) 31 (24–54) 7 completed	Schizophrenia or schizoaffective disorder as defined by DSM-IV; patients must have been stable for 4 weeks prior to study entry and have tolerated oral olanzapine well in the past	Approx. 8 weeks
EW-LOBQ; Complete; Full CSR	To determine pamoic acid exposure following dosing with hydroxyzine pamoate	5 Oct 01 Completed 18 Oct 01	Open-label	hydroxyzine pamoate, 100 mg, PO, administered once on Day 1 and every 6 hours on Days 2 to 4	6 HS (6/0) 30 (25–37) 6 completed	Healthy male subjects, aged 18 to 65.	4 days

[a] Median age for both MDGs was calculated separately for each treatment arm and is available in the EW-LOBE study report.

The PK-population analysis was performed based on the data-set from formal PK studies and sparse data (3255 observations from 621 patients) from clinical Phase III Efficacy/Safety studies: HGKA and HGKB.

- Absorption

Absolute Bioavailability**:**
No investigation of the absolute bioavailability of OP Depot has been conducted by the applicant.

Characterization of the sustained release profile of OP Depot:
The OP Depot is designed to provide a sustained systemic absorption of olanzapine after IM injection. Findings from study LOBO show that a single injection of OP Depot produces a sustained olanzapine delivery into the systemic circulation. Plasma concentrations peak occurs approximately 3 days after injection and steady concentrations are maintained for more than two weeks.
Pilot study LOAZ led to similar results. The apparent half-life was also substantially prolonged compared to the oral or fast-acting IM administration. The apparent elimination half-life was estimated to be approximately 232 hours (about 10 days). Taking into account the terminal half-life of olanzapine by oral route (about 30 hours), it appears clearly that the rate of absorption of OP Depot is

the limiting factor of the elimination. Thus the apparent half-life of elimination is the reflection of the apparent half-life of absorption (flip-flop phenomena).

Relative Bioavailability: Intramuscular OP Depot versus oral and RAIM form:
No formal cross-over designed studies have been conducted. However, Study LOAZ brought few information regarding this aspect as limited number of subjects were investigated with each OP Depot dose (n= 3 for the 10 mg dose). The findings of this study showed a lower bioavailability with the OP Depot, with a 38% decrease of AUC0-∞ observed at comparable administered oral dose (10 mg). The CHMP requested the applicant to comment on the difference in the AUC measurements. The response was that, given the fundamental differences in pharmacokinetics between a sustained-release administration versus an oral administration, and given that the aim of the study was to establish if these two dosage forms would produce a similar magnitude of drug exposure and the variability around the exposure, they did not include the relative bioavailability assessment in the analysis. Study LOAZ was not designed or expected to provide a robust comparison of the relative bioavailability between OP Depot and oral olanzapine. Nevertheless, the resulting pharmacokinetic data from LOAZ showed a high degree of correlation between the oral and OP Depot administrations. The clearance values were nearly identical as well as the intersubject variability of the clearance results, and the AUC values were also highly correlated between the two treatments. The CHMP considered this point resolved.

Interpretation of relative BA *versus* RAIM formulation was hampered by a flaw in the design of study LOBS. In the sequence of periods, the OP Depot period preceded the RAIM period with a possible carry-over effect.

Systemic exposure to olanzapine: OP Depot versus oral route:
Study LOBE provided a picture of the systemic exposure to Olanzapine after repeated-dose of OP Depot following the claimed dosing scheme: dose range 150 up to 405 mg and administration intervals of two and four weeks. The plasma sampling was not optimal to allow an accurate estimation of relevant PK parameters AUCτ, Cmax and Cmin. However, useful information could be obtained. For instance approximate estimation of systemic exposure after repeated administration allows comparison with the oral route. Systemic exposure (AUCτ, Cmax, Cmin) achieved after IM OP Depot administration should be compared to that observed with the oral route at the claimed correspondent dose. Multiple-dose group subjects were dosed for up to 6 months, and two dosing intervals were tested: two weeks and four weeks (main PK parameters are summarised in the tables below).

2-Week Injection Interval Group:

Table 3: Geometric Mean (CV) Steady-State PK Parameters .

Dose (mg)	N_{PK}[a]	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$[b] (hr)	$AUC_{\tau,ss}$ (ng•hr/mL)	$t_{1/2}$[c] (hr)	CL_{ss}/F (L/hr)	V_{ss}/F (L)	$C_{av,ss}$ (ng/mL)	PTF (%)
100[d]	3	13.5 (56.2)	96.0 (95.68 - 167.83)	3530 (46.7)	322 (28.7)	28.4 (46.7)	13700 (82.9)	10.5 (46.7)	73.8 (34.5)
150	12	29.7 (29.0)	48.1 (19.28 - 334.23)	7540 (26.2)	422 (75.8)	19.9 (26.2)	12800 (86.8)	22.4 (26.2)	54.1 (48.5)
160[e]	7	26.1 (63.6)	95.9 (48 - 312)	6870 (51)	352 (189)	23.3 (51.0)	13200 (383)	20.4 (51.0)	82.9 (53.9)
210	17	39.3 (37.7)	48.7 (0 - 190.92)	10400 (46.2)	561 (90.4)	19.2 (46.2)	16300 (73.5)	31.0 (46.2)	50.7 (53.5)
300	19	46.1 (41.7)	82.8 (19.87 - 335.72)	12400 (46.5)	751 (192)	24.1 (46.5)	28300 (168)	37.0 (46.5)	39.5 (42.6)

Abbreviations: $AUC_{\tau,ss}$ = area under the concentration-versus-time curve during one dosing interval at steady state; $C_{av,ss}$ = predicted average olanzpapine concentration at steady state; CL_{ss}/F = apparent plasma clearance at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; N_{PK} = number of subjects used to calculate mean $AUC_{\tau,ss}$, CL_{ss}/F, and $C_{av,ss}$, and may differ slightly for other parameters; PTF = peak-to-trough fluctuation; $t_{1/2}$ = apparent terminal elimination half-life; $T_{max,ss}$ = observed sampling time of $C_{max,ss}$; V_{ss}/F = apparent volume of distribution at steady state.

[a] N_{PK} = number of subjects used to calculate mean $AUC_{\tau,ss}$, CL_{ss}/F, and $C_{av,ss}$, and may differ slightly for other parameters.

[b] Median and range reported.

[c] Prolonged half-life reflects depot absorption.

[d] Parameters estimated for 3rd injection.

[e] Parameters estimated for 2nd or 3rd injection.

4-Week Injection Interval Group:

Table 4: Geometric Mean (CV) Steady-State PK Parameters .

Dose (mg)	N_{PK}[a]	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$[b] (hr)	$AUC_{\tau,ss}$ (ng•hr/mL)	$t_{1/2}$[c] (hr)	CL_{ss}/F (L/hr)	V_{ss}/F (L)	$C_{av,ss}$ (ng/mL)	PTF (%)
210	21	22.8 (57.2)	48 (0 – 503)	9150 (44.7)	553 (87.5)	21.9 (44.7)	18300 (128)	13.6 (44.7)	99.6 (56.5)
255	6	25.4 (44.8)	336 (0 - 503)	12400 (51.5)	718 (102)	20.6 (51.5)	20800 (101)	18.4 (51.5)	50.8 (55.0)
300	14	39.6 (45.2)	167 (44 – 507)	18900 (44.0)	590 (93.3)	15.9 (44.0)	16700 (113)	28.1 (44.0)	79.6 (45.0)
405	29	47.6 (52.5)	96.0 (24 - 669)	23600 (50.0)	995 (110)	17.1 (50.0)	24600 (120)	35.2 (50.0)	65.1 (48.4)

Abbreviations: $AUC_{\tau,ss}$ = area under the concentration-versus-time curve during one dosing interval at steady state; $C_{av,ss}$ = predicted average olanzpapine concentration at steady state; CL_{ss}/F = apparent plasma clearance at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; N_{PK} = number of subjects used to calculate mean $AUC_{\tau,ss}$, CL_{ss}/F, and $C_{av,ss}$, and may differ slightly for other parameters; PTF = peak-to-trough fluctuation; $t_{1/2}$ = apparent terminal elimination half-life; $T_{max,ss}$ = observed sampling time of $C_{max,ss}$; V_{ss}/F = apparent volume of distribution at steady state.

[a] N_{PK} = number of subjects used to calculate mean $AUC_{\tau,ss}$, CL_{ss}/F, and $C_{av,ss}$, and may differ slightly for other parameters.

[b] Median and range reported.

[c] Prolonged half-life reflects depot absorption.

Bioequivalence:
Considering that particles size of the active substance could potentially impact the release and therefore the BA of olanzapine from the IM Depot, the applicant has conducted a study (study LOBS) designed for the investigation the impact of PSD (Particle Size Distribution) on the BA of OP Depot. Four different lots with different particles size were used in the study.
When AUC ratio was considered, the relative bioavailability observed with each OP Depot Lot (single-dose) was quite lower (70-50 %) to that observed with the oral route (steady-state). However, these conclusions should be regarded cautiously as data from steady-state situation (oral route) was compared to data obtained after single-dose (IM Depot). Nevertheless, the comparison made by the applicant could not address the concern regarding the comparability of the BA obtained with different Lots. The CHMP therefore asked the applicant to conduct inter batches comparison and to better present study LOBS results in order to clarify the possible impact of PSD and particles shape on the variability of BA. One problem the applicant identified was that the group of patients that was given four different lots in Study LOBS had a different proportion of patients who smoked. After the model was adjusted for this variable (smoking habit), the four lots tested in LOBS were shown to be substantially equivalent with respect to Cmax and AUC.

Influence of application site on the bioavailability:
No specific investigation of the influence of the site of injection on the BA of olanzapine has been conducted. Nevertheless, comparison of limited data in patients observed after deltoid injection (study LOBE) suggested that no substantial impact of the injection into the deltoid on the bioavailability characteristics of OP Depot may occur compared to the injection into the buttocks.

- Distribution

Distribution pattern of olanzapine has been extensively investigated by oral route. Thus, no specific studies were conducted with the OP-Depot IM formulation. In plasma, olanzapine is highly (approximately 93 %) bound to plasma proteins (albumin and Acid-Alpha1-Glycoprotein). Protein plasma binding is not saturable at therapeutic plasma concentrations level. No significant change in protein binding has been observed in pathologic situation such as sever renal insufficiency.

- Elimination

The metabolism pathway and excretion route of olanzapine and related metabolites has been clearly elucidated with the oral route as well as when olanzapine is administered by IM route (Fast-Acting IM solution). For instance, no new metabolite has been identified with the IM fast-acting solution as compared to the oral route. The overall metabolism profile was similar with both routes of administration.

Considering that a new salt (pamoate) of olanzapine is used in the Depot formulation, the applicant has performed two new studies with OP Depot, study LOBO and study LOBQ, in order to elucidate the metabolite profile of olanzapine and pamoic acid (the counter ion of olanzapine in the new pamoate salt used in the OP Depot as compared to the oral route).

The findings of these studies regarding the metabolite profile of Olanzapine Pamoate as compared to the oral route are summarized below:

Olanzapine:
The primary metabolites of olanzapine (4-N-Desmethyl olanzapine and glucuronide of olanzapine) were present at exposure levels 3-fold to 10-fold lower than unchanged olanzapine following the first and the fourth 300 mg IM dose and after repeated oral olanzapine doses. The PK characteristics of the metabolites following the fourth injection of OP Depot were consistent with the estimates following the first injection, indicating no metabolic unforeseen shift after repeated injection of OP Depot.
Based on the metabolic ratios (a comparison of the AUCτ ss for each metabolite to the oral olanzapine AUCτ), it appears that metabolism of olanzapine is not affected by the route of administration.

Analysis of urine samples from patients receiving oral olanzapine and OP Depot show the presence of Olanzapine, N-Desmethyl olanzapine and 4-N-Oxyde Olanzapine, 2-Hydroxy-methyl Olanzapine and the 4-N-Glucuronide and 10-N-Glucuronide diasteromers of olanzapine. Therefore, Olanzapine-related metabolite profiles for urine and plasma after oral olanzapine and after OP Depot were similar.

Pamoic acid:
Data from study LOBO showed that pamoic acid concentrations were reflecting those of olanzapine and demonstrated the sustained release of the olanzapine pamoate salt from the intramuscular site of injection. Concentrations were similar between the clinical trial material lots. In general, the sustained release of the olanzapine pamoate salt from the intramuscular site of injection yields a later Tmax, lower Cmax, and extended half-life for pamoic acid. No related-acid pamoic derivative has been detected in plasma and only traces of pamoic acid were detected in faeces.
The main PK measures for pamoic acid following the first 300 mg of OP Depot dose are summarised in the table below.

Table LOBO.11.4. Comparison of Geometric Mean (Geometric CV) Pamoic Acid Pharmacokinetic Parameters After the First 300-mg Dose of IM Olanzapine Depot

CT Lot	N_{PK}	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)
Overall	9	189 (80)	72.0 (24 – 335.97)	114000 (127)	500 (145)
CT21907	4	185 (37.1)	120 (24 - 335.97)	116000 (217)	510 (223)
CT501950	5	193 (120)	48.0 (24 - 216)	112000 (92.8)	493 (123)

Abbreviations: $AUC_{0-\infty}$ = area under the time-versus-time curve from zero to infinity; CT = clinical trial; C_{max} = maximum plasma concentration; h = hour; N_{PK} = minimum observed drug concentration during a dosing interval at steady state; t_{max} = time to maximum concentration; $t_{½}$ = apparent terminal elimination half-life.
[a] Median and range reported.

- Dose proportionality and time dependencies

Single Dose:
Information regarding dose proportionality after single dose administration of OP Depot could be obtained from study LOAZ. The dose range of 10 to 40 mg was investigated in a small number of healthy volunteers. Also some information regarding higher doses (50 up to 450 mg) could be obtained from study LOBE.
In study LOAZ a dose proportional increase of AUC_{0-inf} was achieved. However, the CHMP considered that the estimation of AUC0-inf was not optimal and that the dose range tested was far below the dose range of clinical interest (150-405mg).

Repeated Dose:
In study LOBE using clinically relevant OP Depot doses up to 405 mg suggested T½ to be comparable to that in study LOAZ after 100 mg injection, but increasingly higher T½ values were observed after higher doses (2-week data: 210 mg – T½ 561 hours; 300 mg – T½ 751 hours; 4-week data: 405 mg – 995 hours).

Given the above results, the CHMP asked the applicant to discuss upon the non-linearity of absorption kinetics and its clinical implications. The applicant performed a new statistical analysis that confirmed that it is not possible to assert that the pharmacokinetics of olanzapine after single or multiple doses of

OP Depot are dose proportional and linear across the full range of doses. Nonetheless, no major aspects of nonlinearity were revealed in these analyses. Further, the applicant argued that the calculated value of olanzapine clearance remains similar for both OP Depot and orally administered olanzapine. Hence, a longer half-life should not be assumed to be associated with a greater degree of accumulation upon multiple-dose administration, but should be properly associated with a prolonged and sustained concentration profile for olanzapine associated with a rate-limited absorption process.
The CHMP agreed that the dose-proportionality was not demonstrated after single and multiple-dose administration of the OP-Depot, with no major deviation being evidenced. No definite conclusions could be drawn regarding the dose-proportionality due to the high inter-subjects variability and the overlapping between doses.

Time dependency:
Use of the practically insoluble pamoate salt of olanzapine may potentially lead to higher accumulation than expected in the site of injection. Useful information regarding this aspect could be obtained from the findings of studies LOBO and LOBE as plasma concentrations profiles has been established in the same patients after a first-dose and repeated-dose.
The accumulation ratio was estimated to be approximately 2.9 (study LOBO). As at last dose (fourth dose after two months treatment), the steady-state was not reached, the accumulation ratio reported is considered to be an underestimation of the actual accumulation coefficient at steady-state. Better estimation of accumulation ratio could be obtained from data of study LOBE. However, no suitable presentation of the data allowing the evaluation of accumulation coefficient was provided by the applicant. Visual analysis of mean plasma profiles in patients treated with the highest doses 300 mg/2q-weeks and 300-405 mg/q4-weeks showed that steady-state was not reached after 24 weeks treatment. Therefore, higher accumulation may occur after long term use of OP Depot rising safety concern. The CHMP asked the applicant to address these concerns. The requested estimation of the accumulation ratio from LOBE study data was not provided by the applicant. No further discussion of the findings of this study with regard to the drug accumulation (such as analysis of residual plasma concentrations after long term use) was made by the applicant. However, the applicant asserted that no additional accumulation may occur with repeated injections for 24 weeks (6 months) and 100 weeks (two years). This assertion is based on the evaluation performed by the population pharmacokinetic modelling.
This assertion could not be endorsed by the CHMP. Indeed, few long-term data were available and thus included in the database used in the population pharmacokinetic analysis and the validation of the model by external data was lacking. As a consequence, the validity of the predicted systemic exposure after long term use (up to 2 years) was not assured. Therefore, no robust conclusions could be drawn from this analysis with regard to systemic exposure after long-term use. This lack of information should be sought from the perspective that inflammatory reactions and subsequent encapsulation may retain the particles in the tissue much longer than expected. As stated by the applicant, this aspect has not been investigated specifically in the clinical studies. Moreover, when preclinical data are considered, the relatively short-term (8 weeks) investigation in animal models (rats and beagle dogs) after single-dose administration showed some degree of an inflammatory response and encapsulation. No long-term investigations have been conducted in animals.
As a response to CHMP objections, additional data (Olanzapine plasma concentrations after long-term use) from Study HGKB obtained after the initial submission population pharmacokinetic datalock, as well as with a new population dataset from Study LOBE (not available at the time of the initial submission) are submitted. In these additional data, Olanzapine plasma concentrations were obtained for 191 patients (228 concentrations) after 1 year of treatment, for 155 patients (182 concentrations) after 2 years and for 57 patients (59 concentrations) after 2.75 years (33 months).
Neither of these datasets was used in the original population pharmacokinetic model development which included data from Studies HGJZ, LOBS, HGKA and HGKB. The additional long term HGKB data have been used to obtain the Bayesian estimates of the concentrations, and the LOBE data have been used for both Bayesian estimates and model parameters estimation. A good fit between the model estimated and the observed long-term exposure is obtained. The olanzapine plasma concentrations do not increase with time and thus there is no trend suggesting the potential for long-term accumulation. Furthermore, there was no new safety pattern emerging with long-term use of OP Depot.

Intra- and inter-individual variability:
The intrasubject variability was examined in several studies. In Study LOBE, more than 300 profiles for multiple doses of OP Depot were examined for each patient's olanzapine plasma-concentration profile. The results showed a high intersubject and intrasubject variability. The CHMP requested the applicant to discuss the impact of the higher variability on the management of patients during the treatment by IM Depot. The applicant showed that the large intra subject variability was mainly a reflection of inter-occasion variability due to variability in dissolution and absorption from the site of intramuscular injection. On the basis of the applicant's arguments, the CHMP considered this point resolved.

- Special populations

No formal studies were conducted in subjects with renal impairment, hepatic impairment, and in different races since the pharmacokinetic profile in these sub-groups could reasonably be inferred from that resulting from the oral route. No formal studies were conducted in children as OP Depot is not recommended in children and adolescents below 18 years.

Gender:
A gender difference in olanzapine pharmacokinetics is attributed to differences in CYP1A2 enzyme activity. Typical plasma concentrations of olanzapine will likely be higher in females. However small difference is observed and no dosage adjustment is required.

Elderly:
No specific study has been conducted in order to compare the pharmacokinetics of OP Depot in elderly subjects comparatively to young subjects. The applicant states that the different PK behaviour in the elderly (a trend toward lower plasma clearance and a longer mean elimination half-life as shown with oral administration) is attributed to decreased function of organ system responsible for metabolism or excretion. Consequently, the recommendation of use of OP Depot in this sub-group could be inferred from those stated for oral route. Nevertheless, the CHMP asked the applicant to further elaborate on the possible dosing recommendation and on the impact of the reduction and of the biological modifications of the muscular mass in the elderly population. In response, the applicant agreed to include the following information into the SPC section 4.2, *Elderly patients*
ZYPADHERA has not been systematically studied in elderly patients (> 65 years). ZYPADHERA is not recommended for treatment in the elderly population unless a well-tolerated and effective dosage regimen using oral olanzapine has been established. A lower starting dose (150 mg/4 weeks) is not routinely indicated, but should be considered for those 65 and over when clinical factors warrant (see section 4.4). ZYPADHERA is not recommended to be started in patients >75 years.
And the following information appear in section 4.4, *Use in elderly patients (>75 years)*
No information on the use of ZYPADHERA in patients >75 years is available. Due to biochemical and physiological modification and reduction of muscular mass, this formulation is not recommended to be started in this sub-group of patients.

- Pharmacokinetic interaction studies

No new *in vitro* or *in vivo* studies were provided. Potential for interaction of olanzapine was extensively investigated and related data were submitted in the oral file.

Pharmacodynamics

Pharmacodynamic properties of olanzapine were previously well described.
In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5 HT2A/2C, 5-HT3, 5-HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors m1-m5; α-1 adrenergic; and histamine H1 receptors. In a single oral dose (10 mg) Positron Emission tomography (PET) study in healthy volunteers, olanzapine produced a higher 5 HT2A than dopamine D2 receptor occupancy. In addition, a SPECT imaging study in schizophrenic patients revealed that

olanzapine-responsive patients had lower striatal D2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

In the only pharmacodynamic study performed with OP Depot (HGJW), it was shown that D2 receptor occupancy correlates well with the olanzapine plasma concentration reaching mean levels of receptor oocupancy about 60 % during the course of the study. This study is accepted as a bridging study showing that olanzapine plasma concentrations delivered by the intra muscular administration of OP Depot can be expected to produce pharmacodynamic characteristics that can be predicted by plasma concentrations of olanzapine. No further pharmacodynamic studies are needed to support this application.

Clinical efficacy

No formal dose-finding studies were performed. For efficacy studies, doses were selected based on pharmacokinetic results. The applicant has submitted one phase Ib study (LOBE), in which secondary objectives included a determination of acceptable doses of Zypadhera for use in Phase III studies.

To support the efficacy two primary efficacy and safety studies were performed.

Study HGJZ assessed the efficacy and safety of three doses (300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) of Zypadhera in the acute treatment (8 weeks) of schizophrenia. This was a randomized and placebo-controlled study in 404 patients with schizophrenia.

Study HGKA assessed the efficacy and safety of four doses (45 mg/4 weeks, 150 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) of Zypadhera relative to oral olanzapine (10 to 20 mg) in the maintenance treatment (24 weeks) of schizophrenia. This was a randomized active comparator controlled noninferiority study without a placebo arm in 1065 stabilised outpatients with schizophrenia.

For Studies HGJZ and HGKA, supplementation of Zypadhera with oral antipsychotic medication (including oral olanzapine) was not allowed per the protocols.

In addition, to support the long-term safety and efficacy of Zypadhera, an interim analysis of Study F1D-MC-HGKB has been submitted.

Table 1 shows the dose-response and main clinical studies

Table 1. Dose-response studies and main clinical studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
Dose response study									
F1D-EW-**LOBE**	18 study centers	Open-label, single and multiple-dose	Zypadhera: Single-dose gp: 50 to 450 mg Multiple-dose gp: 100 to 405 every 2, 3, or 4 w	Safety, tolerance, PK, dose definition, maintenance of efficacy	281 enrolled 202 unique subjects completed	Single-dose: 28 days Multiple-dose gp: 3 or 6 months	199M 82F (18-66)	Schizophrenia as defined by DSM-IV	Safety
Primary Efficacy Studies									
F1D-MC-**HGJZ**/Full CSR/ Concluded	42 study centers in 3 countries	Double-blind, randomized, placebo-controlled, fixed-dose	Zypadhera: 210 mg/2 wk, 300 mg/2 wk, 405 mg/4 wk Placebo: One injection/ 2 wk	Efficacy superiority, safety and PK	Randomized: Total=404 Zypadhera 300mg/2wk=100 405mg/4wk=100 210mg/2wk=106 Placebo=98 Completed: Total=267 Zypadhera 300mg/2wk=67 405mg/4wk=72 150mg/2wk=72 Placebo=56	8 weeks	285M 119F 41.88 (18.20-74.12)	Schizophrenia as defined by DSM-IV; BPRS score of ≥ 48 (1 to 7 scale) at Visit 1 BPRS score of ≥ 48	Baseline to-endpoint change in PANSS Total score
F1D-MC-**HGKA**/Full CSR/ Concluded	112 study centers in 26 countries	Double-blind, randomized,	**Zypadhera**: 45 mg/4 wk,	Efficacy non-inferiority, maintenance	Randomized: Total=1065 Zypadhera	24 wk	696M 369F	Schizophrenia as defined by DSMIV or	Time to exacerbation of symptoms and

		olanzapine-controlled, fixed-dose	405 mg/ wk, 150 mg/2 wk, 300 mg/2 wk, **Oral OLZ**: 10, 15, 20 mg/day	of efficacy, safety and PK	300mg/2wk=141 405mg/4wk=318 150mg/2wk=140 45mg/4wk=144 Oral OZP=322 <u>Completed</u>: Total=753 Zypadhera 300mg/2wk=107 405mg/4wk=222 150mg/2wk=90 45mg/4wk=76 Oral OZP=258		38.39 (18.10-70.77)	DSM-IV-TR; clinically **stabilized** on a fixed dose of oral olanzapine for 4–8 weeks during Study Period II	exacerbation rates after 24 wk of maintenance treatment
Supportive clinical studies									
F1D-MC-**HGKB**/ Interim aCSR/Study ongoing	128 study centers in 25 countries	Long-term, open label	Zypadhera flexible doses ranging from 45 mg to 405 mg given at 2-, 3-, or 4-wk intervals	Safety, effectiveness, PK	700 to 1500 Planned 880 Enrolled 674 cont. as of 30 June 2006	Up to 4 years	587M 293F 38.87 (17.77-74.30)	Schizophrenia or schizoaffective disorder who previously completed an Zypadhera clinical trial (HGJZ, HGKA, or LOBS)	

- Dose response study

F1D-EW-LOBE(d) (LOBE): to assess the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of an Intramuscular Formulation of Depot Olanzapine (Pamoate Salt) in Stable Schizophrenic Subjects. Secondary objectives of this phase Ib study included a determination of acceptable doses of Zypadhera for use in Phase 3 studies.

METHODS
This was a multicenter, open-label study in subjects who met the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] and who were stable for the last 4 weeks with olanzapine oral treatment.

Objectives
The primary objective was to assess the safety and tolerance of a depot olanzapine formulation after single and multiple doses in subjects with stabilised schizophrenia.

The secondary objectives were:
- To assess the pharmacokinetics of an olanzapine depot formulation following single and multiple administrations in subjects with stabilised schizophrenia.
- To attempt to define acceptable doses for an olanzapine depot formulation for use in phase III studies.
- To evaluate the maintenance of psychiatric control following depot injections of olanzapine; change of scores from baseline on the BPRS and the CGI-S will be monitored and summarised.

Study periods
Study Period I was the baseline assessment period (Visit 1) for all subjects in the study.

Subjects who completed Study Period I and continued to meet the entry criteria at Visit 2 could enter Study Period II. This period was approximately 28 days.

Subjects who completed Study Period I and who continued to meet the entry criteria at Visit 2 could be entered into Study Period III. Study Period III was between 3 and 6 months in length. The dosing intervals were 14, 21, or 28 days.

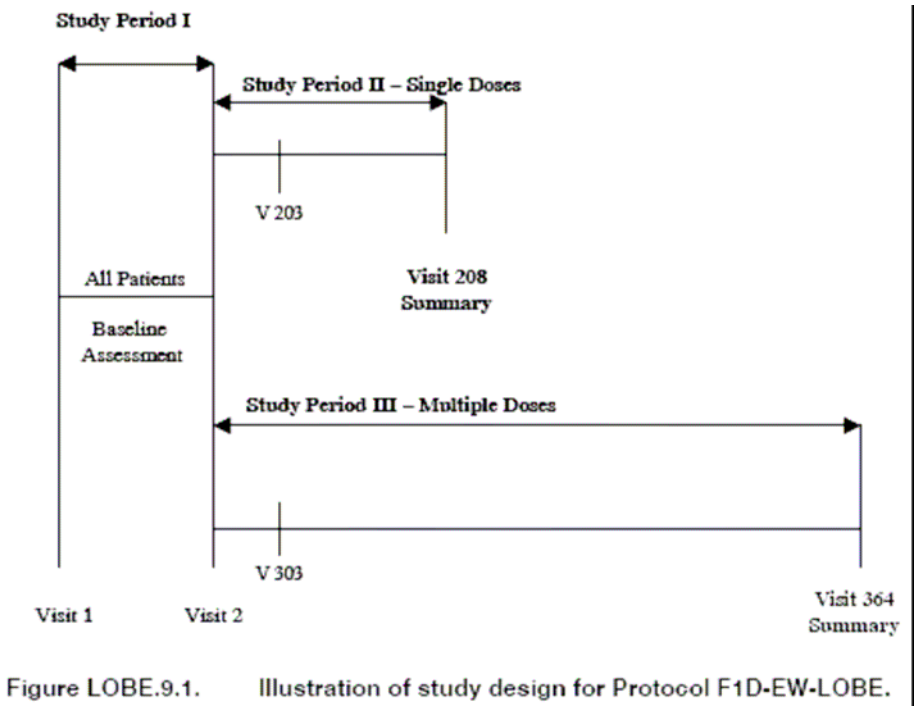


Figure LOBE.9.1. Illustration of study design for Protocol F1D-EW-LOBE.

Study Participants
The main inclusion criteria were:
- Male or female in-subjects or out-subjects at least 18 and no more than 70 years of age.
- Subjects must have schizophrenia (disease diagnostic criteria as defined in DSM-IV)
- Subjects must have been stable for the last 4 weeks (patients must be receiving the same dose of oral olanzapine for the last 4 weeks)
- Subjects must have tolerated oral olanzapine
- An electrocardiogram (ECG) considered within the normal limits, with a QTc interval less than 500 ms, as read from ECG printout.

Treatments

Period I:
The assessment period lasted 4 to 21 days. Subjects continued taking their current oral olanzapine therapy until the last day of the assessment period.

Period II: Single dose
At Visit 2, the first day of Study Period II, subjects had their oral olanzapine discontinued.
Subjects received only one injection ranged from 50 to 450 mg.

Period III: Multiple dose
At Visit 2, the first day of Study Period III, subjects had their oral olanzapine discontinued.
Subjects received injections of 100 to 405 mg, every 2, 3, or 4 weeks for 3 or 6 months.
Once this interval had been determined, it was intended that it remain fixed for each subject throughout Study Period III.
The dose of the subsequent injections could vary depending upon the tolerability and preliminary PK data of the previous injections and new data coming from the ongoing study, as well as from the clinical status of the subject.

Outcomes/endpoints
Safety assessment: vital signs, clinical laboratory tests, and electrocardiograms (ECGs).

Pharmacokinetic assessment: PK assessment blood samples were collected during the oral lead-in and after administering IM olanzapine depot to measure plasma olanzapine concentrations for PK analyses.

Results

Participant flow
Three hundred fourteen subjects entered, and 281 enrolled. Of these 281 enrolled subjects, 202 subjects completed the study according to the protocol. Data from all subjects enrolled are included in the pharmacokinetic (PK) and statistical analyses.
The most common reason for discontinuation from the study was due to subject decision (22 subjects).
A total of 11 unique subjects discontinued the study due to an adverse event (AE).

Thirty-four subjects enrolled in the single dose study (study period II), and 30 subjects completed according to the protocol. Two subjects discontinued due to adverse events (AEs).

Two hundred twenty-three subjects enrolled in the multiple-dose study (study period III), and 153 subjects completed according to the protocol. Seven subjects discontinued due to AEs.

Outcomes and estimation
Following single and multiple doses of IM olanzapine depot, plasma olanzapine concentrations were sustained for at least 28 days.

IM olanzapine depot doses of 150 to 300 mg/2 weeks and 210 to 405 mg/4 weeks were projected to provide average steady-state olanzapine concentrations similar to those obtained following oral administration of 5 to 20 mg/day. Mean plasma olanzapine concentration profiles following repeated administration of IM olanzapine depot showed the steady state was achieved in 2 to 3 months. Details of mean olanzapine concentrations following doses of 150 mg/2 weeks and 405 mg/4 weeks are provided in the two figures below.

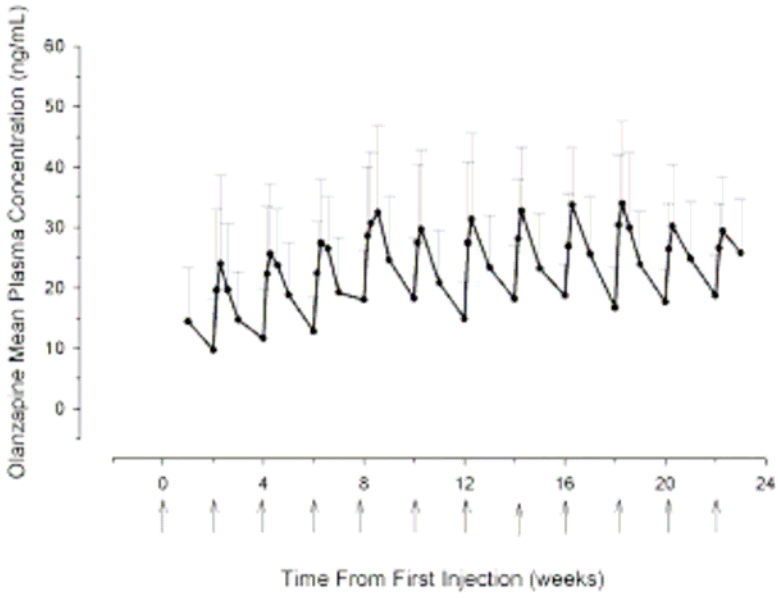


Figure LOBE.11.3. **Mean (+SD) plasma olanzapine concentrations following IM olanzapine depot doses of 150 mg/2 weeks.**

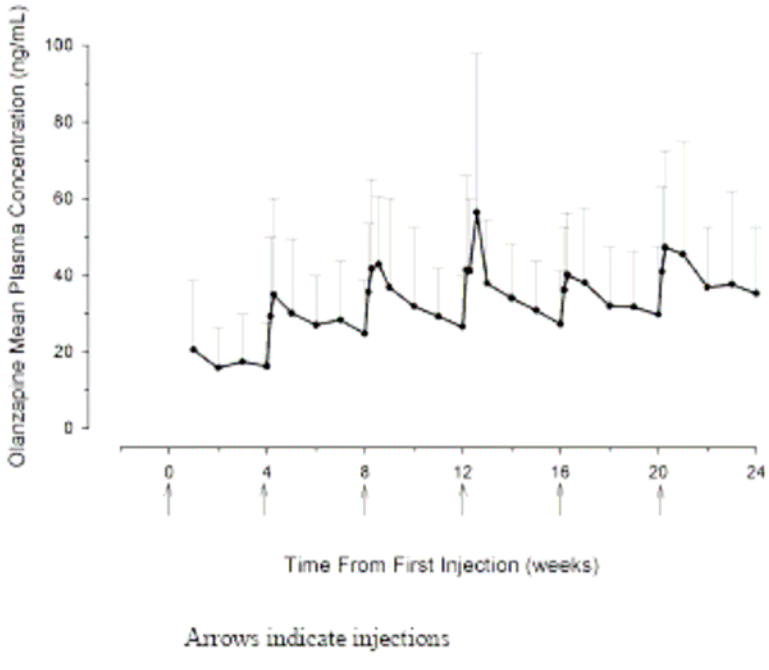


Figure LOBE.11.7. **Mean (+SD) olanzapine plasma concentrations for the Multiple-Dose Group receiving 405 mg/4 weeks.**

- Main study(ies)

HGJZ, 8-week treatment study

METHODS

This was a randomized, double-blind, placebo-controlled, and parallel-design study conducted at 42 centers in 3 countries (United States, Croatia, and Russia).

Study periods

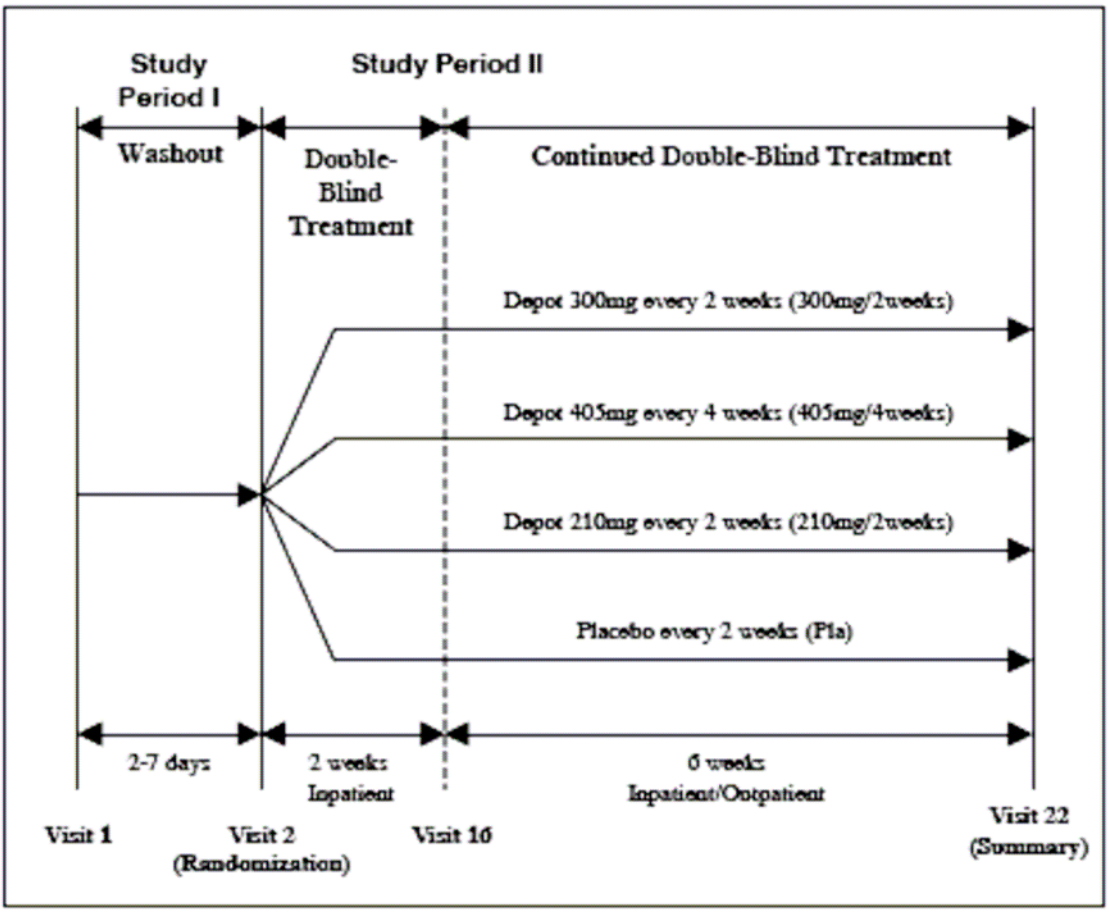


Figure HGJZ.9.1. Illustration of study design for Study F1D-MC-HGJZ.

Study period I: washout period, with duration of 2 to 7 days. Patients were inpatients and were expected to meet all the inclusion/exclusion criteria and complete all examinations prior to entering Visit 2.

Study period II: 8-week double-blind treatment, during which patients received one of four treatment injections every 2 weeks (300 mg/2 weeks, 405 mg/4 weeks, 210 mg/2 weeks, and placebo). Patients who were randomized to 405 mg/4weeks Zypadhera received a placebo injection at every other injection visit. During the first 2 weeks following randomization, patients were expected to be inpatients and were assessed daily.

Study Participants
The main inclusion criteria were:
- Male or female patients at least 18 and no more than 75 years of age.

- Patients must have schizophrenia that meets disease diagnostic criteria as defined in DSM-IV or DSM-IV-TR.
- Patients receiving treatment with an injectable depot antipsychotic must have received the last injection at least 2 weeks or one injection interval, whichever is longer, prior to Visit 2.
- Patients must have a PANSS-derived BPRS score of ≥ 48 (1 to 7 scale).

Main exclusion criteria:
Patients who were previously treated with olanzapine and were considered to be treatment resistant to olanzapine were excluded from participating in the study.

Treatments
Doses evaluated in this study were 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/ 2 weeks Zypadhera in comparison to placebo/2 weeks.

Objectives
The primary objective was to demonstrate superiority of the 3 doses of Zypadhera (210 mg/2 weeks, 405 mg/4 weeks, and 300 mg/2 weeks) compared with placebo in change from baseline to endpoint in the Positive and Negative Syndrome Scale (PANSS) Total score in the acute treatment of patients with schizophrenia.

The secondary objectives were to assess the efficacy, the safety and tolerability of the 3 doses of Zypadhera, to determine the earliest time point at which each doses of Zypadhera show superior clinical improvement, and to characterize the pharmacokinetics (PK) of olanzapine following multiple dosing with Zypadhera.

Outcomes/endpoints
Primary endpoint: change from baseline to endpoint in the Positive and Negative Syndrome Scale (PANSS) Total score (range from 30 to 210, i.e. from symptom not present to symptom extremely severe).

Secondary endpoints:
Efficacy variables:
- PANSS Positive (range from 7 to 49), PANSS Negative (range from 7 to 49), and PANSS General Psychopathology subscales (range from 16 to 112)
- Clinical Global Impression-Severity (CGI-S) and CGI-Improvement (CGI-I) (range from 1 to 7, i.e. from normal to extremely ill)
- Brief Psychiatric Rating Scale (BPRS) (24 items scale, each to be rated in a 7-point scale of severity ranging from 'not present' to 'extremely severe'
- PANSS Total score response rate defined by a 40% or greater decrease in PANSS Total score from baseline to the last value postbaseline

Health outcome/quality of life measures:
- Heinrichs-Carpenter quality of life scale (QLS): The QLS total score is the sum of the 21 items (rate on a 7-point scale with scores 0 and 1 reflect severe impairment). The four categories contained in the QLS are Intrapsychic Foundations (items 13 to 17 plus 20 and 21); Interpersonal Relations (items 1 to 8); Instrumental Role (items 9 to 12); and Common Objects and Activities (items 18 and 19).
- Medical outcomes study 36-items short form health survey (SF-36): this scale (0-100 scale with higher scores representing better health status and functioning) is composed by 36 questions covering 8 areas (physical function, bodily pain, role limitations due to physical problems, vitality, general health perceptions, role limitations due to emotional problems, mental health, and social function)

Safety assessment: Adverse events, Concomitant therapies, Laboratory data, Vital signs, Electrocardiograms (ECGs), Extrapyramidal symptoms (EPS) measured with Simpson-Angus scale (SAS) from 0 complete absence of the Parkinsonian symptoms to 40 presence in extreme form,

Abnormal involuntary movement scale (AIMS) from 0 no dyskinetic movements to 40 severe dyskinetic movements, and Barnes Akathisia scale (Barnes) from 0 no akathisia to 3 severe akathisia.

Sample size
A total of approximately 400 patients had been planned to be randomized, 100 per treatment group.
This sample size had approximately 90% power to detect a difference in means of 10, assuming that the common standard deviation is 21.6 using a two-group t-test with a two-sided α level of 0.05.

Randomisation
Patient numbers were assigned at Visit 1. Randomization of patients to treatment groups was applied within each study site at Visit 2 by a computer-generated random sequence using the Interactive Voice Response System (IVRS) in a 1:1:1:1 ratio into the three Zypadhera groups, and one placebo group.

Blinding (masking)
Study Period I (2-7 days from visit 1 to visit 2) was an open-label washout period.
Study Period II (8 weeks from visit 2 to visit 22) was the double-blind treatment period.

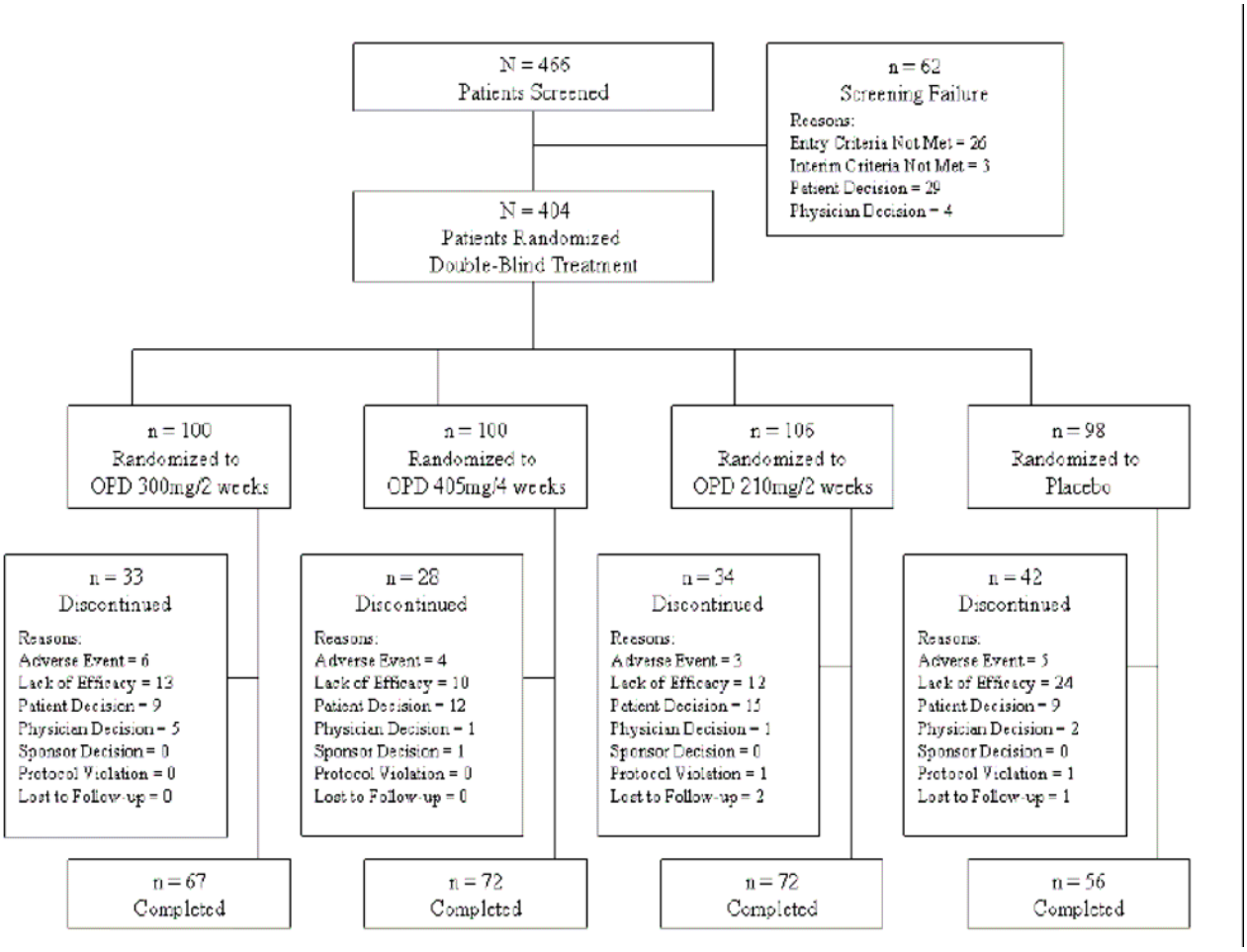
Statistical methods
An intent-to-treat (ITT) principle was applied in the efficacy, safety, and health outcomes analyses. Efficacy analyses included all randomized patients (N=404) with baseline and postbaseline observations. Efficacy data were analyzed using the last-observation-carried-forward (LOCF) method.

Continuous data were analyzed using ANOVA models; the models generally included the terms for treatment and investigator study site. For analysis of proportions, Fisher's exact test was used.

Subgroup analyses were conducted using ANOVA models. All tests of hypotheses were tested at a twosided α level of 0.05. In order to assess longitudinal effects, a likelihood-based repeated measures analysis was conducted on the postbaseline PANSS Total score and associated subscales.

RESULTS

Participant flow
A total of 404 patients began double-blind treatment, and of these, 267 (66.1%) patients completed. The most common reasons for discontinuing the study during this period were lack of efficacy (n=59) and patient decision (n=45). There were no statistically significant differences (p=0.167) across treatment groups for overall reasons for discontinuation.
For the details of the participants flow, see the chart below.



Statistically significant differences in time to discontinuation for lack of efficacy (overall, p=.0154; Zypadhera 310 mg/2 weeks versus placebo, p=.0446; Zypadhera 405 mg/4 weeks versus placebo, p=.0082; Zypadhera 210 mg/2 weeks versus placebo, p=.0161) were seen. Differences in time to discontinuation for any reason and differences in time to discontinuation for AEs were not statistically significant.
The rates of discontinuation were 33% in OPD 300mg/2w group, 28% in OPD 405mg/4w group, 32% in OPD 210 mg/2w group, and 43% in placebo group.

Recruitment
Date first patient enrolled: 22 June 2004.
Date last patient completed: 26 April 2005.

Baseline data
Demographic characteristics:
There were no statistically significant differences between the treatment groups with respect to gender and origin of the patients, the BMI, and the weight. 70.5 % were male and 55.9 % Caucasian, the mean BMI was 28.82 and the mean weight, 85.52 kg.
The mean age of enrolled patients was 40.82 years, with a range of 18 to 74 years.

Illness characteristics:
There were no statistically significant differences with respect to the number of previous episode or exacerbation of schizophrenia in the last 24 months across treatment groups.

Previous antipsychotic use:
There were no statistically significant differences across all treatment groups.
A total of 37.9% of patients had oral olanzapine as previous antipsychotic use.

Numbers analysed
All 404 randomized patients (n=100, Zypadhera 300 mg/2 weeks; n=100, Zypadhera 405 mg/4 weeks; n=106, Zypadhera 210 mg/2 weeks; and n=98, placebo) were included in the primary efficacy analysis.

Outcomes and estimation
Analysis of the primary variable: PANSS Total score
There were statistically significant differences between all treatment groups versus placebo group in change from baseline to endpoint (week 8) in the PANSS Total Score in the treatment of patients with schizophrenia (see Table HGJZ.11.10.).

Table HGJZ.11.10. PANSS Total Score
Visitwise Mean Change from Baseline to Endpoint (LOCF)
Study Period II, F1D-MC-HGJZ

		Baseline	Visit 5 Week 0.43	Visit 9 Week 1	Visit 16 Week 2	Visit 17 Week 3	Visit 18 Week 4	Visit 19 Week 5	Visit 20 Week 6	Visit 21 Week 7	Visit 22 Week 8
300Q2W	n	98	97	98	98	98	98	98	98	98	98
	Mean	102.58	-8.64	-14.80	-19.61	-22.22	-22.68	-23.37	-24.80	-25.79	-26.32
	SE	1.57	1.18	1.54	1.89	2.18	2.25	2.26	2.41	2.42	2.52
	P-value for T-test		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
405Q4W	n	100	100	100	100	100	100	100	100	100	100
	Mean	101.33	-8.22	-13.38	-16.80	-18.84	-20.03	-21.77	-22.49	-22.98	-22.57
	SE	1.44	1.11	1.37	1.63	1.76	1.81	1.90	1.96	2.05	2.21
	P-value for T-test		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
210Q2W	n	106	106	106	106	106	106	106	106	106	106
	Mean	99.55	-7.58	-13.68	-16.51	-19.33	-20.63	-21.82	-22.76	-23.38	-22.49
	SE	1.53	1.20	1.38	1.69	1.70	1.88	1.96	2.03	2.09	2.12
	P-value for T-test		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
PLA	n	98	97	98	98	98	98	98	98	98	98
	Mean	100.60	-5.24	-9.37	-10.97	-10.69	-8.83	-8.74	-8.67	-8.64	-8.51
	SE	1.68	1.03	1.37	1.88	2.15	2.30	2.32	2.27	2.32	2.33
	P-value for T-test		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
ANOVA	Inv Effect	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
	Therapy Effect	.546	.051	.006	<.001	<.001	<.001	<.001	<.001	<.001	<.001
p-Values	300Q2W vs. PLA	.213	.011	.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
	405Q4W vs. PLA	.600	.025	.016	.004	<.001	<.001	<.001	<.001	<.001	<.001
	210Q2W vs. PLA	.991	.056	.005	.003	<.001	<.001	<.001	<.001	<.001	<.001
	300Q2W vs. 405Q4W	.465	.741	.395	.236	.136	.307	.527	.363	.282	.176
	210Q2W vs. 405Q4W	.585	.716	.725	.976	.673	.634	.789	.701	.716	.873
	210Q2W vs. 300Q2W	.201	.488	.607	.242	.274	.574	.708	.588	.466	.226

Abbreviations: 210Q2W = 210mg/2weeks Olanzapine Pamoate Depot, 300Q2W = 300mg/2weeks Olanzapine Pamoate Depot, 405Q4W = 405mg/4weeks Olanzapine Pamoate Depot, PLA = Placebo, n = All randomized patients
Type 3 sum of squares was used in the following ANOVA model: Full model: (Therapy) + (Inv)
Program Location: RMP.F1DSHGJZ.SASPGM(LOPANA1)
Output Location: RMP.F1DO.HGJZ(LOPANA11)

At baseline, the PANSS Total scores in all groups were approximately 100 points, corresponding to patients very symptomatic.
The differences in PANSS Total scale between baseline and endpoint in the three treatment groups (300Q2W, 405Q4W, and 210 Q2W) were respectively -26.32, -22.57, and -22.49 versus -8.51 in placebo group. A mean decrease of 23.8 shows a clinically relevant and important improvement.
The differences were statistically significant from week 0.43 in 300Q2W and 405Q4W treatment groups (respectively -8.64, and -8.22) and from week 1 in 210Q2W treatment group (-13.68).

Analysis of the PANSS Total score response rate
Response was defined as an improvement ≥ 40% of the PANSS Total score at endpoint.
The overall difference in response rate across the four treatment groups (300Q2W, 405Q4W, 210Q2W, and placebo) was not statistically significant different (respectively 25.5%, 20.0, 17.9, and 11.2; p=.075).

Table HGJZ.11.12. PANSS Total Score
Response Rate Analysis (40% Improvement at Endpoint)
Study Period II, F1D-MC-HGJZ

				Fisher's Exact p-Value			
Therapy	N	n	(%)	Overall	405Q4W	210Q2W	PLA
300Q2W	98	25	25.5	.075	.399	.233	.016
405Q4W	100	20	20.0			.725	.117
210Q2W	106	19	17.9				.235
PLA	98	11	11.2				

Abbreviations: 210Q2W = 210mg/2weeks Olanzapine Pamoate Depot, 300Q2W = 300mg/2weeks Olanzapine Pamoate Depot, 405Q4W = 405mg/4weeks Olanzapine Pamoate Depot, PLA = Placebo

Program Location: RMP.F1DSHGJZ.SASPGM(FQRESA1)
Output Location: RMP.F1DO.HGJZ(FQRESA11)

In a post hoc analysis using the decrease of 20% or greater of the PANSS Total score as new definition of response, all 3 Zypadhera dosages again had higher rates of response compared to placebo (60.2%, 56.0%, and 58.5% respectively, compared to 28.6%), and in this analysis the rates were statistically significantly different ($p<0.001$).

Analyses of secondary variables
The differences of score in CGI-I, CGI-S, PANSS Positive, PANSS Negative, PANSS General Psychopathology score, and BPRS were all statistically significant in favour the 3 treatment groups versus placebo.

Health outcomes/quality of life evaluation
Across subscale score mean change, there were no statistically significant differences between Zypadhera and placebo in the analysis of Common Objects and Activities or Instrumental Role.
There were statistically significant differences between Zypadhera and placebo in the analysis of Intrapsychic Foundation and Interpersonal Relations.

SF-36:
All three Zypadhera treatment groups demonstrated statistically significant improvement over the placebo group in the Summary Score-Mental (all three p-values <0.05). There were no statistically significant differences across the treatment groups in the Summary Score- Physical.

HGKA, maintenance treatment study

METHODS
This was a randomized, double-blind, parallel, 24-week outpatient study comparing the efficacy and safety of Zypadhera (150 mg/2 weeks, 405 mg/4 weeks, and 300 mg/2 weeks) with oral olanzapine (10, 15, and 20 mg/day) and with low dose Zypadhera (45 mg/4 weeks). Patients were clinically stabilized with schizophrenia for a minimum of 4 weeks. This study was conducted at 112 study centers in 26 countries (United States, South America, Europe, Turkey, Israel, Taiwan, Australia and Russian Federation).

Study periods

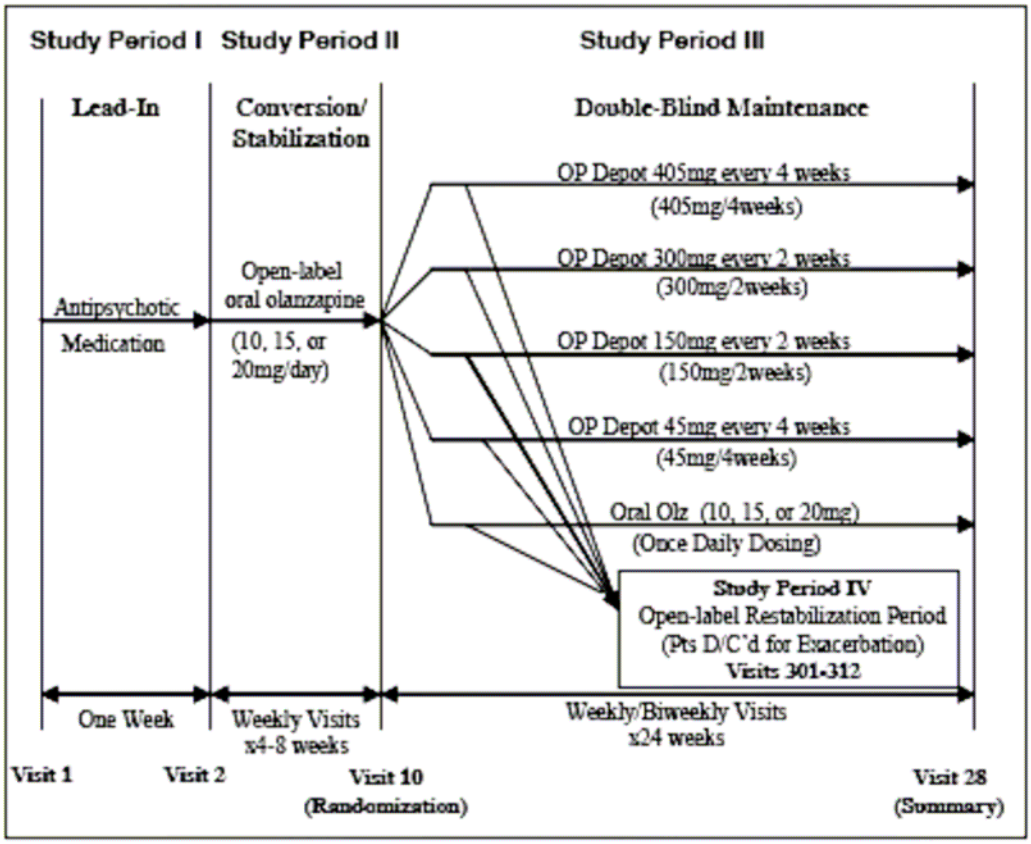


Figure HGKA.1. Illustration of study design for Protocol F1D-MC-HGKA.

Study period I:
Study Period I was the lead-in period and consisted of a minimum of 2 days and a maximum of 9 days.
Patients must continue current oral antipsychotic medication (other than clozapine) during Study Period I.
Patients receiving treatment with an injectable antipsychotic must have received the last injection at least 2 weeks or one injection interval, whichever is longer, prior to Visit 2. Patients taking risperidone long-acting injections must have received their last injection at least 4 weeks prior to Visit 2.

To enter Study Period II, patients must demonstrate clinical stability by the following:
- Outpatient status (long-term residential and chronic care facilities are acceptable)
- A Clinical Global Impression-Improvement of Illness (CGI-I) score of 1, 2, 3, or 4 (when compared with Visit 1 Clinical Global Impression- Severity of Illness [CGI-S] score)
- Brief Psychiatric Rating Scale (BPRS) Positive score ≤ 4 (1 to 7 scale) on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content.

Study period II:
Study Period II is the conversion and stabilization period of the study, during which patients must be discontinued from their current antipsychotic medication and converted to oral olanzapine monotherapy at 10, 15, or 20 mg/day.

Patients who are receiving oral olanzapine monotherapy upon entry into the study must remain in Study Period II for a minimum of 4 weeks and a maximum of 8 weeks.

Patients who are receiving an antipsychotic other than, or in addition to, oral olanzapine upon entry to the study must remain in Study Period II for a minimum of 6 weeks (Visit 8) and a maximum of 8 weeks (Visit 10). This study period will be used as follows:

- 2 to 4 weeks for conversion from current antipsychotic medication to oral olanzapine monotherapy at the discretion of the investigator
- 4 consecutive weeks to meet stabilization criteria as outlined above.

To enter Study Period III, patients must demonstrate stability for 4 weeks (5 consecutive visits), during Study Period II, by meeting the following stabilization criteria:

- No dose change of oral olanzapine monotherapy (fixed at 10, 15, or 20mg/day)
- CGI-I score equal to 1, 2, 3, or 4 (when compared with Visit 1 CGI-S score)
- BPRS Positive score ≤ 4 (1 to 7 scale) on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content.

Study Period III:
Study Period III is the maintenance period consisting of 24 weeks of double-blind maintenance therapy.

Study Period IV:
Study Period IV is the open-label restabilization period for those patients who are discontinued from double-blind therapy in Study Period III due to exacerbation of symptoms associated with schizophrenia.

Study Participants
The main inclusion criteria were:

- Male or female patients at least 18 and no more than 75 years of age.
- Patients must have schizophrenia that meets disease diagnostic criteria as defined in DSM-IV or DSM-IV-TR at the time of study entry.
- Patients receiving treatment with an injectable depot antipsychotic must have received the last injection at least 2 weeks or one injection interval, whichever is longer, prior to Visit 2.
- Stability is present at Visit 1 defined as outpatient status for at least 4 weeks preceding Visit 1, and with BPRS Positive items ≤ 4 (1 to 7 scale). Positive items include conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content.

Patients must not have been previously treated with olanzapine and considered to be treatment-resistant to olanzapine.

Treatments
Doses evaluated in this study were 405 mg/4 weeks, 300 mg/2 weeks, 150 mg/2 weeks, and 45 mg/4 weeks Zypadhera, or oral olanzapine 10 mg/day, 15 mg/day, or 20 mg/day.
Patients randomized to oral olanzapine received the same olanzapine dose that they were stabilized on during Study Period II.
The 45 mg/4 weeks Zypadhera arm (low dose close to placebo) ensured assay sensitivity. This is in line with Appendix to Note for Guidance (CPMP/EWP/49/01, 2003).

Objectives
The first primary objective was to demonstrate noninferior efficacy of Pooled 2-Week Zypadhera (300 mg/2 weeks pooled with 150 mg/2 weeks) as compared with 10, 15, and 20 mg oral olanzapine in terms of exacerbation rates after 24 weeks of maintenance treatment.
The second primary objective was to demonstrate superior efficacy of 300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks as compared to 45 mg/4 weeks in terms of time to exacerbation of symptoms of schizophrenia.

The main secondary objectives were:

- To demonstrate noninferior efficacy in terms of exacerbation rates of Pooled 2-Week Zypadhera (300 mg/2 weeks pooled with 150 mg/2 weeks) compared with 405 mg/4 weeks

- To provide information on transition of patients stabilized on oral olanzapine at 10, 15, or 20 mg/day to therapeutic doses of Zypadhera
- To demonstrate superiority of 300 mg/2 weeks, 150 mg/2 weeks, and 405 mg/4 weeks Zypadhera compared with 45 mg/4 weeks Zypadhera in change from baseline to endpoint in Positive and Negative Syndrome Scale (PANSS) Total score, PANSS Positive, PANSS Negative, and PANSS General subscales
- To assess safety

Outcomes/endpoints
Primary endpoint: Time to exacerbation of symptoms along with the estimated 24 week exacerbation rate.
Exacerbation of symptoms of schizophrenia was defined in this study as follows:
1. An increase on any of the BPRS Positive items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) to a score > 4 and an absolute increase of ≥ 2 on that specific item since randomization at Visit 10, or
2. An increase of any of the BPRS Positive items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) to a score > 4 and an absolute increase of ≥ 4 on the BPRS Positive subscale (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) since randomization at Visit 10, or
3. Hospitalization due to worsening of positive psychotic symptoms.

Secondary endpoints:
Efficacy variables: Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression-Severity (CGI-S) and CGI-Improvement (CGI-I).

Health outcome/quality of life measures: Heinrichs-Carpenter quality of life scale (QLS) and Medical outcomes study 36-items short form health survey (SF-36).

Safety assessment: adverse events, concomitant therapies, laboratory data, vital signs, electrocardiograms (ECGs), extrapyramidal symptoms (Simpson-Angus scale (SAS) from 0 complete absence of the Parkinsonian symptoms to 40 presence in extreme form; Abnormal involuntary movement scale (AIMS) from 0 no dyskinetic movements to 40 severe dyskinetic movements; Barnes Akathisia scale (Barnes) from 0 no akathisia to 3 severe akathisia).

Sample size
The total number of randomized patients was expected to be approximately 1050 patients at a 2:1:1:1:2 ratio in 5 treatment groups: 405 mg/4 weeks, 300 mg/2 weeks, 150 mg/2 weeks, 45 mg/4 weeks, or oral olanzapine.
The sample size of 300 patients in the Pooled 2-Week Zypadhera (300 mg/2 weeks pooled with 150 mg/2 weeks) and 300 patients in the oral olanzapine treatment groups ensured with 90% probability that the 2 groups would be declared noninferior under the assumptions that: 1) the true 6-month exacerbation rate of oral olanzapine is 0.15 and the true 6-month exacerbation rate of Pooled 2-Week Zypadhera was no worse than 0.20; and 2) the discontinuation rate for reasons other than exacerbation is <0.35 for both treatment groups up through 24 weeks on study drug.

For the superiority analyses, the sample size of 150 patients in individual Zypadhera treatment groups had approximately 90% power to detect a hazard ratio of 0.45 between 2 groups, assuming that the discontinuation rate for reasons other than exacerbation was <0.35 for both treatment groups up through 24 weeks on study drug.

Randomisation
Randomization was performed at a 2:1:1:1:2 ratio into 5 treatment groups: 405mg/4weeks, 300mg/2weeks, 150mg/2weeks, 45mg/4weeks, or oral olanzapine.

Patient identification numbers were assigned at Visit 1. Randomization to treatment group was applied within each study site, stratified by oral olanzapine dose at the time of stabilization (10 mg or 15/20

mg/day). Assignment to treatment group at Visit 10 was determined by a computer-generated random sequence using an Interactive Voice Response System (IVRS).

Blinding (masking)
Study Periods I and II were not blinded. Study Period III was the randomized, double-blind portion of the study.

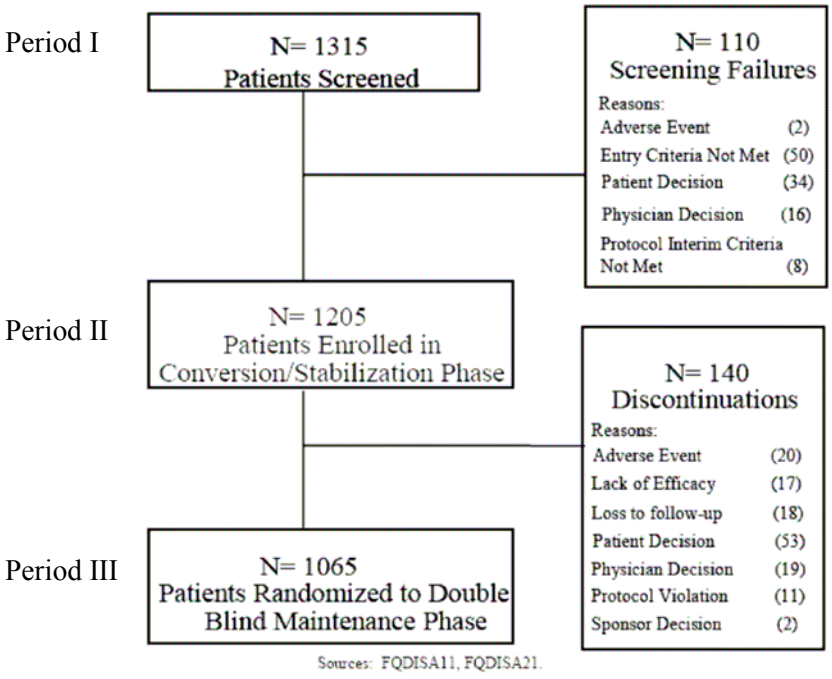
Statistical methods
All analyses were conducted on an intent-to-treat (ITT) basis. Efficacy analyses included all randomized patients (N=1065) with baseline and postbaseline observations unless otherwise stated.
Non-inferiority analyses were based on Kaplan-Meier estimated 24-week (168 days) cumulative exacerbation rates.
Exacerbation was defined as a BPRS Positive item score > 4 (1-7 scale) either with an increase of ≥ 2 points since randomization or with a BPRS Positive subscale increase of ≥ 4 points since randomization, or as hospitalization due to worsening of positive symptoms.
Non-inferiority was assessed using the upper limit of a two-sided 95% confidence limit for the difference between estimated exacerbation rates, with non-inferiority declared if the absolute value of the upper limit was < 0.20.
The delta of 0.20 was based on results of Study F1D-MC-HGGI (Olanzapine Relapse Prevention Versus Placebo in the Treatment of Schizophrenia) and also on comments received from the Committee for Proprietary Medicinal Products (CPMP) during scientific advice.
The CPMP suggested that the true placebo versus oral olanzapine difference in exacerbation rates should be conservatively estimated by the lower limit of an 80% confidence limit on the difference observed in Study HGGI. In this study, the Kaplan-Meier estimated exacerbation rate at Day 182 for placebo was 0.552 and for oral olanzapine was 0.055.
The associated standard errors for these estimated exacerbation rates were 0.106 and 0.019, respectively, for placebo and oral olanzapine. Assuming that the difference between estimated exacerbation rates is approximately normally distributed, this leads to a one-sided 80% lower confidence limit of 0.406 for the difference in exacerbation rates at Day 182.

For time-to analyses, Kaplan-Meier curves were compared using a log-rank test.
Baseline to endpoint analyses used last-observation-carried-forward (LOCF) methodology unless otherwise specified.
Analysis of variance (ANOVA) models were used to evaluate continuous data and generally included terms for treatment and investigator or geographic region.
The analysis of covariance (ANCOVA) on the LOCF mean 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 proportions, the Fisher's exact test was used unless otherwise specified. All hypotheses were tested at a two-sided α level of 0.05.

RESULTS

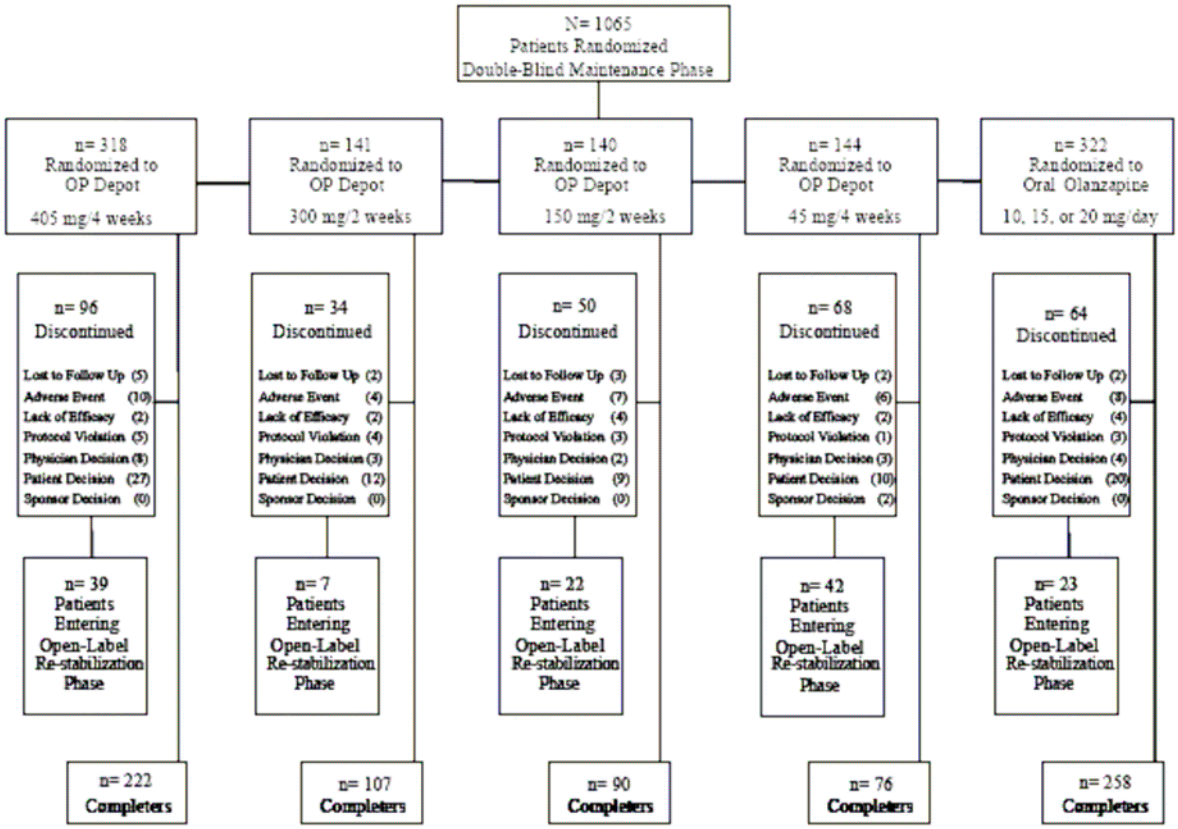
Participant flow
Of the 1205 patients entering the Conversion/Stabilization Phase, 1065 eligible patients were randomized in a 2:1:1:1:2 ratio to receive double-blind Zypadhera (405 mg/4 weeks [n=318], 300 mg/2 weeks [n=141], 150 mg/2 weeks [n=140], 45 mg/4 weeks [n=144]) or oral olanzapine (n=322), respectively, during the Double-Blind Maintenance Phase (Study Period III). A total 753 of the 1065 eligible patients (70.7%) completed Study HGKA.

During the Conversion/Stabilization Phase, the most common reason for discontinuing was patient decision (n=53).



Sources: FQDISA11, FQDISA21.

Figure HGKA.10.1. Patient Disposition From Lead-In/Screening to Double Blind Maintenance Phase.



Source: FQDISA31.

Figure HGKA.10.2. Patient disposition from randomization.

Discontinuation for clinical relapse during double-blind maintenance phase
The rates of discontinuation were 30 % in OPD405 group (p=.003, versus oral olanzapine), 24 % in OPD300 group, 36% in OPD150 group (p<0.001, versus oral olanzapine), 47% in OPD45 group and 20% in oral olanzapine group.
According to the Rate of patients who discontinued study for clinical relapse, oral olanzapine (7.1%) treatment shows statistical difference with OPD150 group (15.7%) and OPD405 group (12.3%); and OPD300 group (5.0%) shows statistical difference with OPD150 group (15.7%) and with OPD405 group (12.3%).

Recruitment
Date first patient enrolled: 6 July 2004.
Date last patient completed: 13 September 2006.

Baseline data

Study period II
Approximately 45% of patients were stabilized on an oral olanzapine dose of 10 mg/day, 22% on a dose of 15 mg/day, and 33% on a dose of 20 mg/day. For patients subsequently randomized to the double-blind maintenance phase, the mean duration of treatment in the conversion/stabilization phase was approximately 4 weeks. It should be noted that 23.3% of these patients in period I entered the study period II already on oral olanzapine therapy.

Study period III
The patient population was predominantly male (65.4%) and Caucasian (71.8%), and included patients aged 18 to 71 years with a mean age of 38.96 years at baseline of the double-blind maintenance phase (study period III) and a mean BMI of 26.89 (14.33-56.49).
There were no statistically significant differences across treatment groups with respect to baseline physical characteristics.
No statistically significant differences were observed between the Pooled 2-Week Zypadhera and the oral olanzapine treatment groups with respect to baseline physical characteristics.

The mean PANSS Total score for all randomized patients was 55.87. Statistically significant differences across treatment groups were observed for the PANSS Total (p=.048), PANSS Negative Total (p=.027), and BPRS Negative (p=.014). On each of these measures, the 45 mg/4 weeks Zypadhera group had the highest mean scores, while the 150 mg/2 weeks group had the lowest mean scores. Baseline CGI-S of Illness scores for all randomized patients were also statistically significantly different across treatment groups (p=.016), again with the 45 mg/4 weeks group having the highest mean score, but with the 300 mg/2 weeks group having the lowest mean score.
These baseline differences between groups were within a range of 3.42 points on the PANSS Total, 1.06 points on the PANSS Negative, 0.62 on the BPRS Negative, and 0.19 on the CGI-S and were therefore not considered clinically meaningful by the applicant.

Numbers analysed
A total of 1065 patients met stabilization criteria and were randomized in a 2:1:1:1:2 ratio to receive Zypadhera at fixes doses of 405 mg/4 weeks (n=318), 300 mg/2 weeks (n=141), 150 mg/2 weeks (n=140), 45 mg/4 weeks (n=144) or to remain on their stabilization dose of oral olanzapine (n=322) for up to 24 weeks of double-blind maintenance therapy.
All analyses were conducted on an intent-to-treat (ITT) basis. Efficacy analyses included all randomized patients (N=1065) with baseline and postbaseline observations unless otherwise stated.

Outcomes and estimation

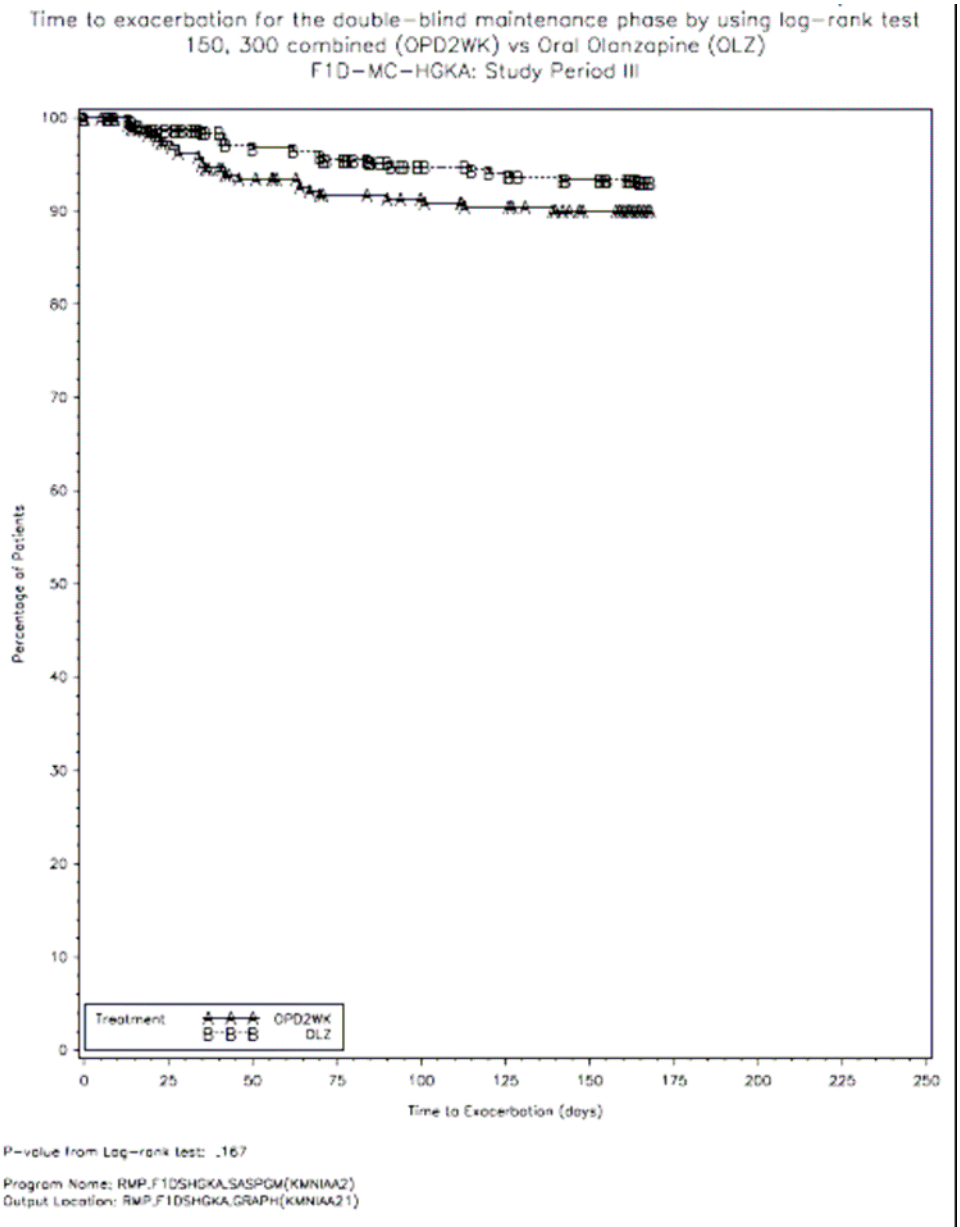
Primary efficacy results

Non-inferiority analysis: comparison of the Pooled 2-Week Zypadhera and the oral olanzapine treatment groups with respect to exacerbation rates.

Table HGKA.11.24. Noninferiority Analysis of Kaplan-Meier Estimates of Exacerbation Rates for Pooled 2-Week OP Depot Versus Oral Olanzapine at 24 Weeks Double-Blind Maintenance Phase

Therapy	Survival Rate	Standard Error	95% CI
OLZ	0.93	0.015	(0.90, 0.96)
OPD2WK	0.90	0.019	(0.86, 0.94)
OLZ - OPD2WK	0.03	0.024	(-0.02, 0.08)

OLZ=Oral Olanzapine
OPD2WK=Pooled 2-Week Olanzapine Pamoate Depot



P-value from Log-rank test: .167

Program Name: RMP.F1DSHGKA.SASPGM(KMNIAA2)
Output Location: RMP.F1DSHGKA.GRAPH(KMNIAA21)

Figure HGKA.11.1. Time to exacerbation for the double-blind maintenance phase (pooled 2-week OP depot versus oral olanzapine).

Superiority analyses: comparisons of time to exacerbation of symptoms for each of the higher Zypadhera doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) versus the low Zypadhera dose (45 mg/4 weeks).

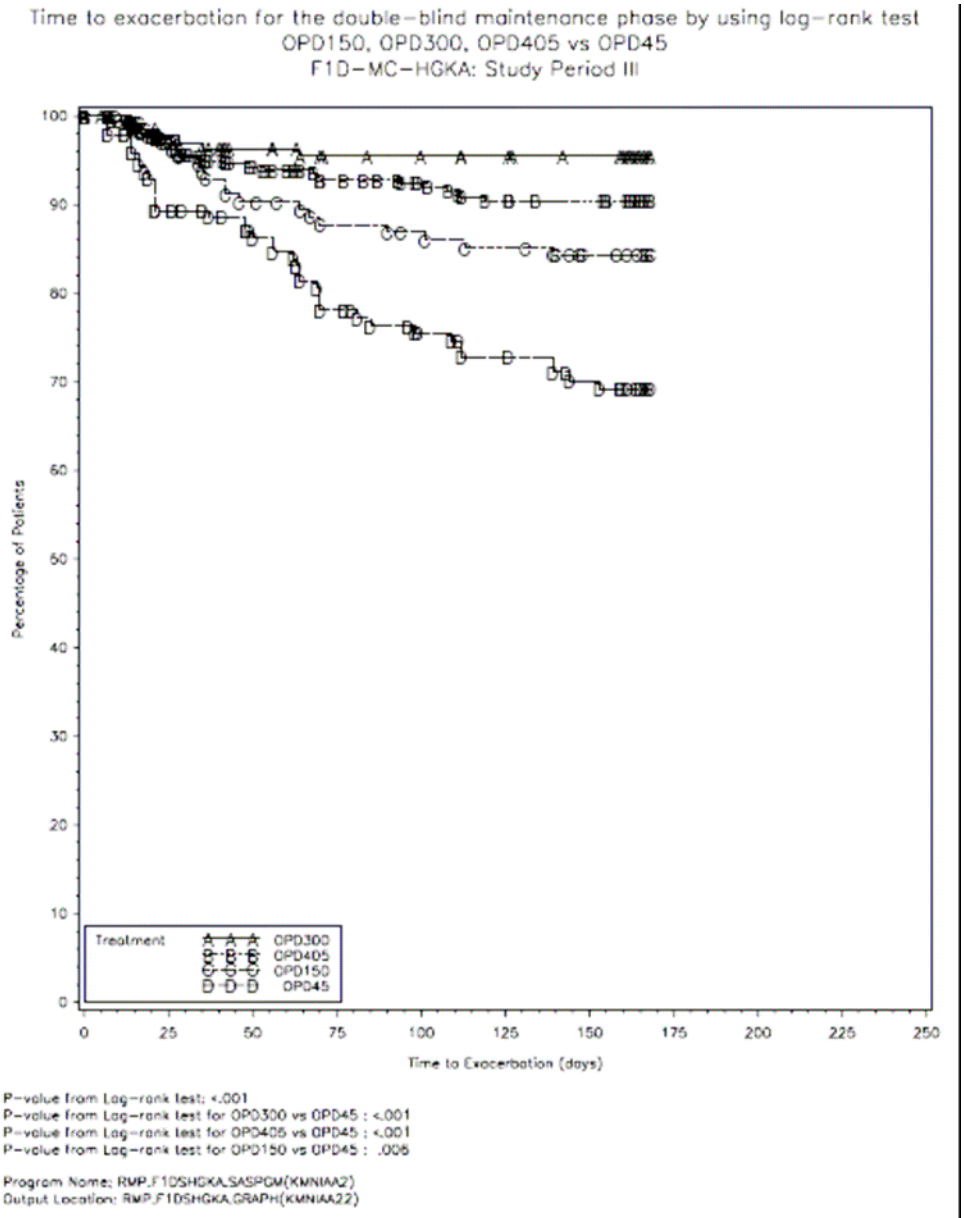


Figure HGKA.11.2. **Time to exacerbation for the double-blind maintenance phase (higher doses of OP depot versus low-dose OP depot; log-rank test).**

Non-inferiority between the pooled 2- week Zypadhera group and the oral olanzapine group was observed on the exacerbation rates (respectively, 90, and 93%, 95% CI [-0.02, 0.08]).
Analysis of time to exacerbation (p=0.167) (Table HGKA.11.24 and Figure. HGKA.11.1.) shows non-inferiority between the pooled 2- week Zypadhera group and the oral olanzapine group.
The analysis of the time to exacerbation shows superiority of the OPD405, OPD300 and OPD150 on the OPD45 group (Figure HGKA.11.2.).
Thus, the two primary objectives of the maintenance study were reached.

Secondary efficacy results
Analysis of exacerbation rates shows non-inferiority between the pooled 2- week Zypadhera and OPD405, and between OPD405 and oral olanzapine group.

The oral olanzapine treatment group was statistically significantly superior to the Pooled 2-Week Zypadhera treatment group on the mean change of the PANSS Total scores (p=0.019) after 24 weeks. After 24 weeks, the mean PANSS Total score was 55.82 (+ 0.24) on the Pooled 2-Week Zypadhera treatment group and 53.57 (-2.52) on the oral olanzapine. This difference could be considered as non-clinically significant as a score of 55.82 after 24 weeks confirms maintenance of treatment.

Considering the mean change of the PANSS Total scores for each group of treatment, OPD300 (-2.19) and oral olanzapine (-2.52) treatment groups are superior to Zypadhera 150mg (+2.66) (respectively, p=0.014 and p < 0.001) and oral olanzapine treatment group is superior to Zypadhera 405 (-0.09) (p=0.008).

- Ancillary analyses

Analyses of Relative Risk of Exacerbation
The risk of exacerbation of symptoms for patients stabilized at 10 mg oral olanzapine is 2.08 times higher for patients in Zypadhera 150mg/2weeks group, and seems maintained for patients in Zypadhera 405mg/4weeks group (HR=1.03). The risk of exacerbation of symptoms for patients stabilized at 15 or 20 mg oral olanzapine seems maintained for patients in Zypadhera 300mg/2weeks group (HR=1.01).

Analyses of Switch from Oral Olanzapine Treatment to Zypadhera Treatment
A statistically significant difference was observed in the log-rank test comparison across treatment groups (p-value=0.017). For patients stabilized on 10 mg/day oral olanzapine, approximately 98% of those randomized to the 300 mg/2 weeks Zypadhera treatment group completed the double-blind maintenance phase without experiencing an exacerbation event, compared to 93% of patients in the 405 mg/4 weeks Zypadhera and oral olanzapine treatment groups, 86% of patients in the 150 mg/2 weeks Zypadhera treatment group, and 82% of patients in the 45 mg/4 weeks Zypadhera treatment group.

Data from patients stabilized on 10 mg/day oral olanzapine during the conversion/ stabilization phase suggest that switching patients from 10 mg/day oral olanzapine to 300 mg/2 weeks, 405 mg/4 weeks, or 150 mg/2 weeks Zypadhera has no statistically significant effect with respect to relative risk of exacerbation compared to remaining on oral olanzapine.
For patients stabilized on 15 or 20 mg/day oral olanzapine during the conversion/stabilization phase, the relative risk of exacerbation was 2.5 times higher in the 150 mg/2 weeks Zypadhera treatment group versus the oral olanzapine treatment group, suggesting that patients stabilized on 15 or 20 mg/day oral olanzapine should be switched to an Zypadhera dose higher than 150 mg/2 weeks. However, switching patients from 15 or 20 mg/day oral olanzapine to 300 mg/2 weeks or 405 mg/4 weeks Zypadhera showed no statistically significant effect with respect to relative risk of exacerbation compared to remaining on oral olanzapine.

The plasma concentration of the depot-preparation is build up rather slowly i.e. steady state is only reached after several months with the risk of under-dosing and as a consequence early treatment failure. The rate of discontinuation was 20% in the oral olanzapine arm, 24 % in the Zypadhera 300mg/2weeks group, 30 % in the Zypadhera 405mg/4weeks group, 36% in the Zypadhera 150mg/2weeks group and 47% in the Zypadhera 45mg/2weeks arm.
In the higher Zypadhera group most exacerbations occurred early, during the first 50 days, suggesting that even the highest dose 405 mg/4weeks injection may not be as effective as oral olanzapine in maintaining good response.
The hazard ratios for exacerbations depot versus oral olanzapine were in favour of the oral comparator (except for the Zypadhera 300mg/weeks where responses are inconsistent).

On the basis of the above concerns, the CHMP asked the applicant to discuss upon the increased risk of exacerbation with Zypadhera 150mg/2weeks and on the proposed dose correspondence scheme for the switch from oral olanzapine to Zypadhera.

The applicant argued that the study design of HGKA favoured the oral olanzapine group because subjects who were stabilised, and therefore responding, on a certain oral dose where randomly switched to an Zypadhera dose that could be less or greater than the preceding oral dose. As requested by the CHMP, analyses examining hazard ratios indicating relative risk of exacerbation in comparison to oral olanzapine and to 45 mg/4 weeks Zypadhera at 2 months time were also conducted.
The analyses indicated that patients were at greater risk of exacerbation during the first 2 months of treatment with Zypadhera. The initial period of switching to a depot is therefore an important juncture in treatment that inherently carries a greater risk of exacerbation than does any subsequent period of treatment. For this reason, the applicant suggested that for patients whose target oral olanzapine dose would be 10 or 15 mg/day, clinicians should initiate Zypadhera treatment at a dose higher than 150mg/2 weeks As a consequence, an appropriate dosing scheme is included in section 4.2 of the SPC. The CHMP accepted as valid the argumentation of the applicant.

- Analysis performed across trials (pooled analyses and meta-analysis)

No analyses across trials were performed.

- Clinical studies in special populations

No studies in special populations were performed.

- Supportive study(ies)

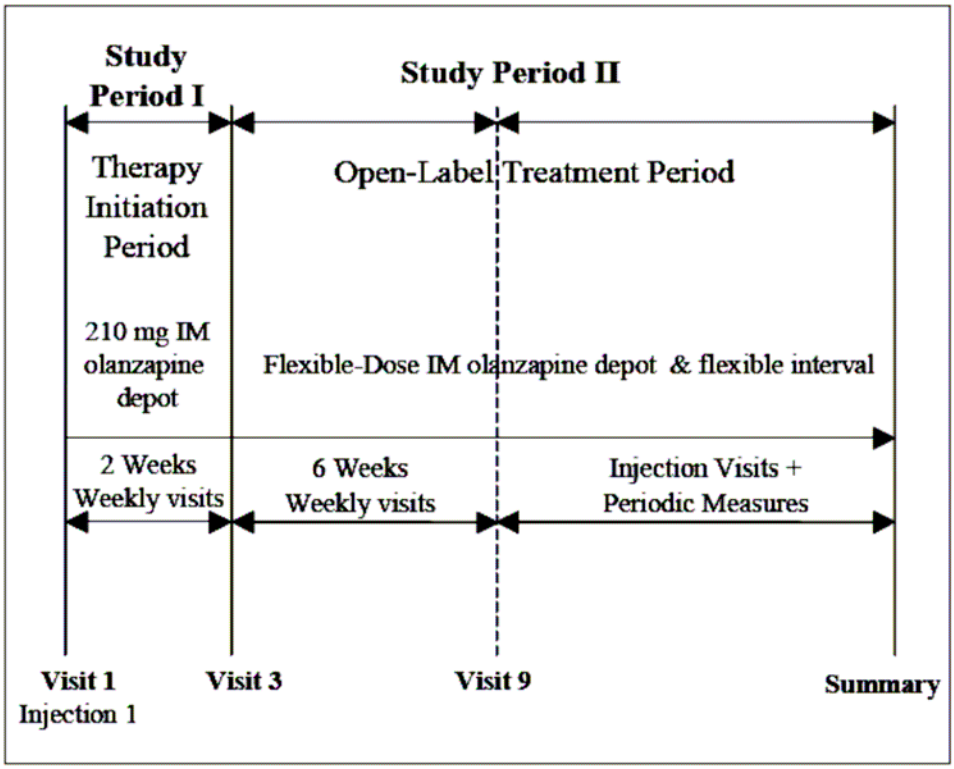
F1D-MC-HGKA SPIV: A Double- Blind Randomized Study Comparing Intramuscular Olanzapine Depot to Oral Olanzapine and Low-Dose Intramuscular Olanzapine Depot in the Maintenance Therapy of Patients with Schizophrenia: Study Period IV

A total of 133 patients with schizophrenia who were discontinued from double-blind therapy in Study Period III due to exacerbation of symptoms were entered into the 24-week restabilization period (Study Period IV). Patients were predominantly male (66.2%) and Caucasian (74.4%), with a mean age of 40 years. Mean body mass index (BMI) was 26.95, and mean weight was 76.88 kg. Concomitant medication was used by 95 (71.4%) patients, with the most common medications being lorazepam (n=27, [20.3%]), clonazepam (n=23 [17.3%]), and biperiden (n=14 [10.5%]).

The modal dose of open-label oral olanzapine for the restabilization period for most patients (89 [66.9%]) was 20 mg/day. The most common reasons for discontinuation for the 80 patients who discontinued Study Period IV were physician decision (n=30 [22.6%)]) and lack of efficacy (n=20 [15.0%]). A total of 53 (39.8%) patients completed Study Period IV, with completion defined as 24 weeks of treatment or restabilization, whichever came first. The mean time patients participated in Study Period IV was 116 days.

Improvement was seen in mean CGI-I scores over the course of the study period, decreasing from a mean of 4.81 (n=128) at Visit 301 to a mean of 3.53 at Visit 312 (n=57), indicating mild improvement on average. For CGI-S scores, statistically significant improvements from baseline were observed at each visit (Visit 301, p=.037; all other visits, p<.001).

F1D-MC-HGKB: An Open-Label Study of Intramuscular Olanzapine Depot in Patients with Schizophrenia or Schizoaffective Disorder (interim analysis)
This is an open-label extension study lasting up to 4 years for patients who completed one of the following three prior Zypadhera studies: F1D-EW-LOBS, HGJZ, or HGKA. The study is still ongoing, but an interim analysis of this study is included in this application to support the long-term safety and efficacy of Zypadhera.
The study design is presented below.



Note: In Protocol HGKB, OP Depot was called IM olanzapine depot.

Figure HGKB.5.1. Illustration of study design for Protocol F1D-MC-HGKB.

A total of 133 patients with schizophrenia who were discontinued from double-blind therapy in Study Period III due to exacerbation of symptoms were entered into the 24-week restabilization period (Study Period IV). Patients were predominantly male (66.2%) and Caucasian (74.4%), with a mean age of 40 years. Mean body mass index (BMI) was 26.95, and mean weight was 76.88 kg. Concomitant medication was used by 95 (71.4%) patients, with the most common medications being lorazepam (n=27, [20.3%]), clonazepam (n=23 [17.3%]), and biperiden (n=14 [10.5%]). The modal dose of open-label oral olanzapine for the restabilization period for most patients (89 [66.9%]) was 20 mg/day. The most common reasons for discontinuation for the 80 patients who discontinued Study Period IV were physician decision (n=30 [22.6%)]) and lack of efficacy (n=20 [15.0%]). A total of 53 (39.8%) patients completed Study Period IV, with completion defined as 24 weeks of treatment or restabilization, whichever came first. The mean time patients participated in Study Period IV was 116 days.

Improvement was seen in mean CGI-I scores over the course of the study period, decreasing from a mean of 4.81 (n=128) at Visit 301 to a mean of 3.53 at Visit 312 (n=57), indicating mild improvement on average. For CGI-S scores, statistically significant improvements from baseline were observed at each visit (Visit 301, p=.037; all other visits, p<.001).

Treatment emergent adverse events (TEAEs) were reported in 42 (31.6%) patients. The most frequently reported TEAEs were depression (n=5 [3.8%]), hypertension (n=4 [3.0%]), acute psychosis (n=3 [2.3%]), headache (n=3 [2.3%]), psychotic disorder (n=3 [2.3%]), and thinking abnormal (n=3 [2.3%]). Nine (6.8%) patients discontinued Study Period IV because of AEs. No deaths were reported during this study period. Thirty-two patients (24.1%) experienced a serious adverse event (SAE) in Study Period IV. The most frequently reported SAEs were psychotic disorder (n=9 [6.8%]), schizophrenia (n=8 [6.0%]), acute psychosis (n=4 [3.0%]), delusion (n=2 [1.5%]), hallucination (n=2 [1.5%]), and suicidal ideation (n=2 [1.5%]).

During Study Period IV, potentially clinically significant (PCS) weight gain, defined as an increase of ≥7% over baseline weight, was observed in 6.6% of patients; a statistically significant mean increase

2.6 kg) from baseline to LOCF endpoint was observed for weight (p=.002). Treatment-emergent abnormal laboratory values at any time observed in >10% of patients were low mean cell hemoglobin concentration (MCHC [14.7%]), high LDL cholesterol (33.3%), and high prolactin (28.6%). Medical conditions or adverse events in Study Period IV resulted in hospitalization of 18% of patients, with a mean of 2.4 days spent in hospital. Primary study conditions or psychiatric conditions resulted in hospitalization of 47% of patients, with a mean of 1.1 days spent in hospital. Overall, oral olanzapine at a daily dose of 10, 15, or 20 mg for up to 24 weeks was well tolerated by patients who experienced exacerbation of their schizophrenia symptoms during Study Period III. Overall improvement from baseline in both mean CGI-I and mean CGI-S scores was observed throughout the study period.

- Discussion on clinical efficacy

Characterisation of the pharmacokinetic profile of Zypadhera represented one of the main issues of this application.
Zypadhera showed a lower bioavailability with respect to the oral route, whereas one would expect to have lower bioavailability with the oral administration due to first-pass effect. The applicant argued that interpretation of those data should take into account that study LOAZ was not designed to provide a robust comparison between the bioavailability of oral olanzapine and Zypadhera. Nevertheless, a high degree of correlation between the two formulations was detected. Comparison with the RAIM form was hindered because of a shortcoming in the design of study LOBS. In fact, in the sequence of periods, the OP Depot period preceded the RAIM period with a possible carry-over effect.

Another concern of the CHMP was the non linearity of the absorption kinetics and its clinical implications. In fact, repeated administration of clinically relevant Zypadhera doses resulted in increasingly higher $T_{1/2}$ values. The applicant argued that the calculated clearance remained similar for both oral olanzapine and Zypadhera, thus the prolonged half lives should not be assumed to be associated with a greater degree of accumulation upon multiple-dose administration, but should be properly associated with a prolonged and sustained concentration profile for olanzapine associated with a rate-limited absorption process.
The CHMP concluded that despite the claim of the applicant that the increase of observed $T_{1/2}$ is not in relation with a decrease in the clearance of olanzapine, a local accumulation in the site of injection could not be excluded. Also the findings of the population PK analysis as initially presented by the applicant couldn't lead to a robust conclusion with regard to the systemic exposure after long-term use. At the end of the procedure, the applicant submitted new PK long-term data from the ongoing study HGKB. Olanzapine plasma concentrations were obtained for 191 patients (228 concentrations) after 1 year of treatment, for 155 patients (182 concentrations) after 2 years and for 57 patients (59 concentrations) after 2.75 years (33 months). The olanzapine plasma concentrations do not increase with time and there is no trend suggesting the potential for long-term accumulation reflected. Furthermore, there was no new safety pattern emerging with time. The CHMP concluded that concern on accumulation risk was solved.

No specific study has been conducted in order to compare the pharmacokinetics of Zypadhera in elderly subjects comparatively to young subjects. However, the CHMP asked the applicant to further elaborate on the possible dosing recommendation and on the impact of the reduction and of the biological modifications of the muscular mass in the elderly population. In response, the applicant agreed to include specific recommendation for the dosing regimen in elderly patients into section 4.2 of the SPC.

Two primary efficacy and safety studies were performed.

In study HGJZ (8-week randomized placebo controlled superiority study**),** three doses were evaluated, 300 mg/2weeks, 405 mg/4weeks and 210 mg/2weeks, whereas the 150 mg/2weeks dose was not assessed although it was included in the dosing scheme as initiation treatment corresponding to 10mg oral olanzapine. Further to a request of the CHMP to discuss the initiation treatment schedule in view of the missing data, the applicant agreed to remove the 150 mg/2 weeks dose from the initiation schedule.

At the end of the study LOCF analysis showed that all treatments (including placebo) had resulted a statistically significant decrease in PANSS total score from baseline. Mean decreases in PANSS total scores compared to placebo arm were as follows:
Zypadhera 300 mg/2 weeks: 17.81 points ($p<0.001$)
Zypadhera 405 mg/4 weeks: 14.06 points ($p<0.001$)
Zypadhera 210 mg/2 weeks: 13.98 points ($p<0.001$)

All Zypadhera treatments were superior to placebo from week 1 visit on and continued to be more effective through-out the study period. None of the Zypadhera treatments were superior to any one of two other Zypadhera treatments. In Zypadhera arms, mean total PANSS score reduction (LOCF) ranged from 22.3% (405 mg/4 weeks) to 25.7% (300 mg/2 weeks).

After 1 week (Visit 9) of double-blind treatment, patients randomized to the three Zypadhera doses had sustained lower PANSS Total scores than patients randomized to placebo and LS mean change remained significantly superior for all three Zypadhera groups compared with placebo through the completion of the study. At Visit 22 (week 8), Zypadhera 300 mg/2 weeks was superior to Zypadhera 405 mg/4 weeks and 210 mg/2 weeks.

The overall difference in response rate in the study period II across the four treatment groups was not significantly different ($p=.075$).

All three Zypadhera treatment groups showed statistically significant improvement demonstrated on the CGI-I score compared with placebo at Visit 5 (day 3) and throughout the rest of Study Period II. All three Zypadhera treatment groups were statistically significantly superior to placebo in OC visitwise comparisons of the CGI-I score at Visit 5 (day 3) and thereafter. All three Zypadhera treatment groups were statistically superior to placebo in mean change of the PANSS Positive score by Visit 5 (Day 3) and maintained significance through the remainder of the study.

Overall study HGJZ demonstrated superiority over placebo of Zypadhera 300 mg/2 weeks, 405 mg/4 weeks and 210 mg/2 weeks in terms of decreased total PANSS from baseline after 8 weeks treatment in patients with schizophrenia and a PANSS-derived BPRS score of ≥ 48 (1 to 7 scale) at baseline not previously considered to be treatment-resistant to olanzapine.

Study HGKA, a non-inferiority study versus oral olanzapine with placebo arm (45 mg/4 weeks low dose close to placebo, which ensure sensitive assay), assessed the efficacy and safety of three doses (150 mg/2 weeks, 300 mg/2 weeks, and 405 mg/4 weeks) of Zypadhera relative to oral olanzapine (10 to 20 mg) in the maintenance treatment (24 weeks) of schizophrenia.
Patients treated with 10 mg, 15 mg or 20 mg oral olanzapine were then randomized in 45mg/4w, 150mg/2w, 405mg/4w or 300mg/2w OPD group or kept the same oral dose of olanzapine.
The randomization is necessary but introduces a bias into the double-blind comparison by creating an advantage for the randomly assigned oral olanzapine group that remained on its previous dose before and after randomization. Actually, patients stabilized by oral olanzapine at 20 mg/day may be randomized in the OPD 150mg/2 weeks group, while patients randomized in oral olanzapine group would continue to receive the same efficacious and well tolerated dose.
The primary noninferiority analysis in Study F1D-MC-HGKA was a comparison of the Pooled 2-Week Zypadhera and the oral olanzapine treatment groups with respect to exacerbation rates. The analysis showed Zypadhera in the pooled 2-week group analysis to be noninferior to oral olanzapine (10-20 mg).

Non-inferiority between the pooled 2- week Zypadhera group (300 mg/2 weeks and 150 mg/2 weeks) and the oral olanzapine group was observed on the exacerbation rates (respectively, 90 and 93%; 95% CI [-0.02, 0.08]).
Analysis of time to exacerbation ($p=0.167$) showed non-inferiority between the pooled 2- week Zypadhera group and the oral olanzapine group.

The analysis of the time to exacerbation shows superiority of the Zypadhera 405 mg/4 weeks, 300 mg/2 weeks and 150 mg/2 weeks (OPD405, OPD300 and OPD150) versus the 45 mg/4 weeks (OPD45) group, thus the two primary objectives of the maintenance study were reached.

No difference was observed between the Pooled 2-Week Zypadhera treatment group and the 405 mg/4 weeks Zypadhera treatment group with respect to survival (from exacerbation) rate, which was 90% for each group (95% CI for Δ: -0.05, 0.05;). Therefore, the Pooled 2-Week Zypadhera treatment group was noninferior to the 405 mg/4 weeks Zypadhera treatment group with respect to exacerbation rates at 24 weeks after randomization.

Taking into account the principle of zero difference in risk (that is, clinically non significant) between a given oral dose and a given OP Depot dose as opposed to a statistically nonsignificant difference and in order to assess relative risk of relapse in Study HGKA, hazard ratios (HRs) were calculated for each OP Depot dose group relative to the patients who were randomized to remain on their oral dose. Hazard ratios provide the likelihood of an event happening in a test group relative to the likelihood of it happening in a reference group. In this case, the event is relapse, the reference group is the oral olanzapine group (that is, those patients randomized to stay on their oral dose), and the test group is an OP Depot dose group. If the likelihood of relapse in an OP Depot dose group is the same as the oral olanzapine group, the HR will be 1.0. However, if the likelihood of relapse in the OP Depot dose group is greater than that for oral olanzapine, the HR will be greater than 1, with the value reflecting how many times more likely the event is to occur in a given time frame. If the likelihood of relapse in the OP Depot dose group is lower than that for olanzapine, the HR will be less than 1. Therefore, a hazard ratio sufficiently close to 1.0 represents a dose which best approximates the efficacy of the oral dose in question and which is therefore the best starting dose when switching from that oral dose.
Zypadhera treatment groups were statistically significantly superior to the 45 mg/4 weeks Zypadhera treatment group with respect to hazard ratios of exacerbation. With a loading dose of 150 mg/ 2 weeks, patients have a 2 times higher risk to relapse than with 10 mg oral olanzapine, while with a loading dose of 405 mg/4 weeks, patients have the same risk to relapse (HR=1.08 at 2 months and 1.03 at 6 months) than with 10 mg oral olanzapine. Furthermore, patients with a loading dose of 300 mg/2 weeks have the lower risk to relapse at 6 months when switching from 15 mg oral olanzapine.

Switching from oral treatment without a need to supplement with oral dosing would require sufficient (and comparable to oral dosing) efficacy starting from the first injection. For this reason, the CHMP asked the applicant to argue on the possible increased risk of exacerbation during the first months of treatment. The applicant suggested that for patients whose target oral olanzapine dose would be 10 or 15 mg/day, clinicians should initiate Zypadhera treatment at a dose higher than 150mg/2 weeks. As a consequence, an appropriate dosing scheme is included in section 4.2 of the SPC. This dosing scheme also prevents that higher doses than the currently approved might be administered. In fact, it is indicated that the combined total dose of olanzapine from both formulations should not exceed the corresponding maximum oral olanzapine dose of 20 mg/day.

The applied indication for Zypadhera initially was,

Treatment of schizophrenia. ZYPADHERA is effective in the treatment of patients who have previously been exposed to oral olanzapine.

Maintenance treatment of schizophrenia. ZYPADHERA is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response to oral olanzapine.

According to the Appendix to Note for Guidance on the clinical investigation of medicinal products in the treatment of schizophrenia – Methodology of clinical trials concerning the development of depot preparations of approved medicinal products in schizophrenia (CPMP/EWP/49/01, 2003), "Depot preparations are meant for maintenance treatment, once a patient is stabilised satisfactorily on an oral preparation. Therefore a patient usually will continue on the product that has been shown to be effective for him. It would be very rare to start a patient on a depot preparation, as e.g. dose titration is

not possible, an acute effect may be needed or undesirable effects may occur, in which case the preparation cannot be withdrawn".
Results of study HKJZ (8-week randomized placebo controlled superiority study) are consistent with the above statement, as they demonstrate that Zypadhera starts to be effective in the treatment of schizophrenia episodes from week 1, after the acute phase, and the steady state is reached not before 8 weeks.
Based on the above reasons, the CHMP considered that the indication proposed was not adequate, and further to additional discussion with the applicant the following indication was eventually agreed,

Maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

In addition, the below changes to the SPC sections 4.2 and 4.4 were agreed to ensure that the use of Zypadhera be limited to eligible patients only (patients already treated with oral olanzapine; no acute exacerbation treatment).

Section 4.2:

"Patients should be treated initially with oral olanzapine before administering ZYPADHERA, to establish tolerability and response".

Section 4.4:

"ZYPADHERA should not be used to treat patients with schizophrenia who are in an acutely agitated or severely psychotic state such that immediate symptom control is warranted".

Clinical safety

- Patient exposure

In the analysis of exposure data (see table below), the total number of patients is 1778, whereas in the analysis of Treatment Emergent Adverse Events (TEAEs), the total number of patients is 1779. This difference is due to 1 patient (HGJZ-47-5037) who was randomized to Zypadhera (Placebo-Controlled Database [HGJZ]), but discontinued study participation prior to the first injection. All available data (for example, AEs, vitals, etc.) for this patient are included in the safety analyses as applicable. The total number of patient exposures (1778) and the unique number of patient exposures (1719) presented in this summary are sufficient to meet the requirements of the ICH E1 guidelines on the extent of population exposures to assess clinical safety (ICH 1994). At the time of datalock for this application, 445 patients had received at least 1 continuous year of treatment with Zypadhera. Among these 445 patients, 98.1% of the doses received by patients were equal to or greater than 150 mg.

Patient exposure

Databases/Studies	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range
Placebo-Controlled Database/ Study HGJZ	404 patients randomized for up to 8 weeks	Pooled Zypadhera treatment groups = 305 patients Placebo=98 patients	210mg/2 weeks=106 300mg/2 weeks=99 405mg/4 weeks=100
Olanzapine-controlled Database/ Study HGKA	921 patients randomized for up to 24 weeks	Pooled Zypadhera (excluding 45mg/4 weeks) treatment groups = 599 patients Oral Olanzapine = 322 patients	150mg/2 weeks =140 300mg/2 weeks=141 405mg/4 weeks=318
Overall Integrated Database/ Studies HGJW-LOBE-LOBO-LOBS-HGJZ-HGKA-HGKB	1778 patients who received treatment with Zypadhera	Pooled Zypadhera treatment groups = 1778 patients	150mg/2 weeks =238 210mg/2 weeks=983 300mg/2 weeks=697 405mg/4 weeks=785

- Adverse events

Sedation was the only AE reported statistically significantly (p=.036) more often in Zypadhera-treated patients (8.2%) than in placebo-treated patients (2.0%). Sedation is a common TEAE reported historically with oral olanzapine. The incidence of sedation seen in patients treated with Zypadhera in the Placebo-Controlled Database was lower than that typically seen with oral olanzapine and most likely reflects the fact that 37.9% of the patients in study HGJZ had previous exposure to olanzapine and that the vast majority (94.1%) had previous exposure to 1 or more antipsychotic agents. Note, sedation reported as a TEAE does not include IAIV injection events described elsewhere (special topic report for IAIV injection events (see later on). In all other events for which a statistically significant between-group difference was observed, the reported incidence was higher in the placebo group compared with Zypadhera.

In the Olanzapine-Controlled Database no statistically significant overall difference between groups was observed in the incidence of patients with 1 or more TEAE (p=.147). There were statistically significant differences between groups in the incidence of chest pain (p=.005), menstrual disorder (p=.043), parkinsonism (p=.042), and rhinitis (p=.042); although all of these events were reported only by patients receiving oral olanzapine. These findings appear to be spurious and do not imply a substantial difference in the safety profile of the 2 olanzapine formulations.

In the Overall Integrated Database the most frequently reported TEAEs in 5% or more of patients were insomnia (10.8%), weight increased (8.4%), anxiety (7.8%), headache (7.3%), somnolence (6.7%), and injection site pain (5.5%). All of these events, except injection-site pain (expected with an injectable product) and headache (common in clinical trials), are consistent with events observed historically in patients treated with oral olanzapine or with symptoms of the disease state.

The incidence and severity of treatment-emergent injection-site–related AEs were compared between patients treated with Zypadhera and patients treated with placebo in the Placebo-Controlled Database. Incidence and severity of treatment-emergent injection-site–related AEs were also summarized for Zypadhera patients in the Overall Integrated Database. The key findings from these analyses were as follows: 1) The 11 injection-site–related AEs in the Placebo-Controlled Database were all reported by Zypadhera-treated patients. Of these events, 7 were reported to be related to injection-site pain, with 6 reported to have a maximum severity of “mild” and 1 reported to be “moderate.” 2) In the Overall Integrated Database, 8.5% of Zypadhera-treated patients reported 1 or more injection-site–related AEs. Injection-site pain was the most frequently reported event (5.5%). All other injection-site–related AEs occurred in <1% of patients. Overall, injection-site–related AEs occurred at a low rate and the majority were reported to be of “mild” severity. The rate of these events was generally consistent with rates reported in other products intended for IM administration. The most common injection-site–related AE in either database was injection-site pain, which was reported by most patients as “mild” in

severity. Four patients (4/1779, 0.2%) discontinued study participation because of injection-site–related AEs.

- Serious adverse event/deaths/other significant events

One death was reported across all Zypadhera studies (1/1779, 0.056%) in the Overall Integrated Database. This death was considered by the investigator to be unrelated to study drug or to study procedures. Additional 2 deaths have occurred in the ongoing studies Study HGKB and 1 death occurred in Study HGLQ (Patient HGLQ-300 3022). These 3 deaths occurred after the data cut-off date for this application (30 June 2006), precluding written narratives. Two of the deaths were in patients receiving Zypadhera, whereas the other death occurred in a patient receiving oral olanzapine. According to the Lilly Safety System (LSS) report, 2 of the deaths were unrelated to study drug or study procedures (1 death due to sepsis, 1 death due to leptospirosis). The third death was due to heart failure but relatedness to treatment is unknown.

Serious AEs
In Placebo-Controlled Database nineteen patients reported one or more SAEs. Most events were reported only once. Events reported in 2 or more patients in either treatment group included 4 reports of psychotic disorder in the Zypadhera group and 2 reports of schizophrenia (1 in Zypadhera and 1 in placebo). There was an additional report of schizophrenia, paranoid type, in an Zypadhera-treated patient. By event, none of the SAEs were reported statistically significantly more often in the Zypadhera group compared with the placebo group. Forty-two patients in the Olanzapine-Controlled Database reported 1 or more SAEs. Most events were reported only once. Serious AEs reported in 2 or more patients in either treatment group included schizophrenia (n=8), acute psychosis (n=5), psychotic disorder (n=4), aggression (n=2), and paranoid type schizophrenia (n=2); all events that are consistent with symptoms of the underlying disease. None of the SAEs were reported statistically significantly more often in the Zypadhera group than in the oral olanzapine group. A total of 159 (8.9%) patients experienced 1 or more SAEs. Most events were reported only once. Serious AEs reported in 5 or more patients included psychotic disorder (n=34; 1.9%), schizophrenia (n=31; 1.7%), agitation (n=7; 0.4%), suicidal ideation (n=7; 0.4%), anxiety (n=6; 0.3%), auditory hallucination (n=6; 0.3%), paranoia (n=6; 0.3%), paranoid schizophrenia (n=5; 0.3%), and suicide attempt (n=6; 0.3%). Consistent with the controlled databases, all of these events are associated with symptoms of the underlying disease.

IAIV events

Cases of inadvertent intravascular injection (IAIV) were reported by the applicant within the initial submission. The new cases that occurred after the submission of the application were also submitted and discussed.
The events presented with signs and symptoms consistent with olanzapine overdose which included dizziness, confusion, disorientation, slurred speech, altered gait, weakness or reduced level of consciousness ranging from mild sedation to coma.

For the cases submitted initially, based on an estimated 25,716 injections, the inadvertent intravascular (IAIV) injection events (16) have occurred in 0.06% of injections. For the 11 events in which time to onset of symptoms was specified, the onset was within the first hour for 10 events, ranging from immediately after an injection to 45 minutes. The time to onset for the 11th event was 90 minutes. None of the IAIV injection events involved sudden onset of profound sedation or incapacitation; instead, all began with milder symptoms, which progressed to more severe symptoms in some events. In general, the later the onset of symptoms, the slower their progression. All patients fully recovered from the events, and the majority continued to receive further injections of Zypadhera.

Lists of all IAIV injection events occurring up to 30 April 2007 were presented. A total of 19 events were listed of which 5 were classified as definite, 8 as probable, 5 as possible and 1 as unlikely. Time of onset after the injection ranged from immediate to within 60 min in those events that were listed as definite. In other 14 cases time of onset ranged from 5 min to 2 hours 45 min.

In an event of IAIV, one would expect the onset of symptoms to be from immediate to a few minutes. The fact that e.g. in a well documented case the onset of symptoms was 45 min after the injection and coincided with a high peak concentration is concerning. Upon request of the CHMP the applicant has discussed other possible mechanism than IAIV that may explain the delay in symptoms. They include mechanisms by which the suspension comes into contact with blood. These other imaginable mechanisms (other than IAIV) discussed in the response represent conditions that can explain dose dumping with certain amount of delay after the injection. It is however reassuring that the incidence of these events reported in the studies was roughly similar to that that has been reported for IAIV of penicillin G procaine and that the root cause seems not to be within the quality of the manufactured product. However, these mechanisms are only assumptions, gathering information from future IAIV injection and other related events leading to very high peak concentrations is essential.

New IAIV cases: On 28th February 2008, the applicant informed the CHMP of 3 further cases reports of patient with an inadvertent intravascular event (IAIV). One of this IAIV was with onset occurring >3 hours post-injection. This new case which originated in Mexico has been investigated by the applicant's clinicians and it would appear that the onset of the IAIV did occur later than 3 hours post-injection and before 5 hours, but a more precise timing was not possible.

As of 30 May 2008, a total of 29 IAIV injection events have been identified in 28 patients during OP Depot clinical trials. Based on more than 40,000 OP Depot injections given to 2054 patients in clinical trials through 30 May 2008, IAIV injection events have occurred in approximately 0.07% of injections, or 1.4% of patients.

According to these findings, the onset of signs and symptoms may be between 5 minutes and <5 hours, and the symptomatology very likely might represent a medical emergency. As a consequence, the CHMP requested the applicant to adopt adequate measures for monitoring the patients after the administration of Zypadhera.
The following measures were agreed:

- After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours.
- Patients should be accompanied to their destination after the observation period.
- Patients should be informed that they should not drive or operate machinery for the remainder of the day of the injection.
- Patients should pay attention for signs and symptoms of an IAIV injection event and be able to obtain assistance if needed for the remainder of the day of the injection.

The risk of IAIV events will also be addressed by the RMP.

The CHMP also recommended that the term IAIV should be replaced by the term "Post injection syndrome" in future materials, as this terminology would maybe draw more efficiently the attention of the prescribers on the risks associated with these administrations.

- Laboratory findings

In the Placebo-Controlled Database statistically significant differences in mean changes were observed between treatment groups for the following laboratory analytes: monocytes, eosinophils, creatinine, sodium, albumin, cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, total bilirubin, and direct bilirubin. For each analyte, the absolute mean change was generally very small. Though the difference between groups was not statistically significant, Zypadhera-treated patients showed a significant within-group decrease of -5.80 µg/L and placebo treated patients showed a non-significant within-group decrease of -4.11 µg/L in prolactin. With respect to prolactin level, this decrease was not unexpected because many patients in this group received previous antipsychotic medications (39.4% with risperidone and 25.7% with haloperidol prior to randomization to Zypadhera or placebo, and as some of these medications have a greater effect on prolactin (David et al. 2000).

A statistically significant between-treatment group difference was observed for low leukocyte count (p=.003); 4/94 (4.3%) placebo-treated patients had low leukocyte counts compared with 0/293 (0.0%) of Zypadhera-treated patients. Although not statistically significant between groups, 35/160 (21.9%) Zypadhera-treated patients had high prolactin levels at endpoint compared with 7/47 (14.9%) placebo-treated patients. This finding was not unexpected and is consistent with the Olanzapine Core Data Sheet, which states that increases in prolactin are very common and have been seen in 34% of olanzapine treated patients in historical placebo-controlled studies.

In the Olanzapine-Controlled Database statistically significant differences were observed between treatment groups for eosinophils, GGT, and sodium; although none of these differences were clinically meaningful. With respect to prolactin, small and clinically insignificant mean decreases were observed at endpoint in both treatment groups (Zypadhera [-1.90 µg/L] and oral olanzapine [-1.79 µg/L]).

In the Overall Integrated Database statistically significant within-treatment group changes were observed for hemoglobin, mean cell hemoglobin (MCH), leukocyte count, segmented neutrophils, monocytes, MCV, ALKPH, creatinine, calcium, potassium, fasting glucose, nonfasting glucose, total bilirubin, and prolactin. These changes were very small increases or decreases, and not clinically meaningful. A statistically significant mean decrease in prolactin (-.09 µg/L) was observed at endpoint.

The incidence of patients with abnormal high or low ALT/SGPT values and potentially clinically significant changes (PCS) in ALT/SGPT values was examined for all 3 databases. An additional analysis of the incidence of patients with ALT/SGPT elevations 3 or more times the ULN was evaluated for the Placebo-Controlled Database. In this analysis, changes >3 x ULN in ALT/SGPT values were observed in 2.7% (8/291) of patients treated with Zypadhera compared with 3.2% (3/94) of patients treated with placebo. None of these patients experienced jaundice. Review of case report form data revealed that in 3 of these patients, liver enzymes reverted to the normal range despite continued treatment, and in 5 patients enzyme values decreased but were still above the normal range at the end of therapy. In the analysis of clinically significant changes in the Overall Integrated Database, 1614 patients had baseline ALT/SGPT levels ≤90 U/L. The incidence of ALT/SGPT elevations to >200 U/L was 0.7% (12/1614). Again, none of these 12 patients experienced jaundice or other symptoms attributable to liver impairment, and most had transient changes that tended to normalize while olanzapine treatment was continued. Among the 1778 exposures in Zypadhera clinical trials, about 0.4% (7/1778) of patients who discontinued study participation did so because of transaminase increases. None of these 7 patients had jaundice.

In the analysis of PCS changes in CPK levels, 39/1618 (2.4%) of Zypadhera-treated patients met the criteria for high CPK levels. Ten of these patients had CPK levels greater than 5000 U/L. Although some elevation of CPK levels would be expected as a result of the trauma caused by an IM injection, the case report forms for these 10 patients with very high levels of CPK were carefully reviewed. Three had documented possible causes for the elevated CPK level (seizure, exercise, and a fall), while the remaining 7 cases had no easily identified cause. Most very high elevations in CPK were transient and later returned to lower levels. There were no reports of rhabdomyolysis or neuroleptic malignant syndrome (NMS) in any of the patients in Zypadhera studies.

In the mean change analyses, prolactin levels in both the Placebo- and Olanzapine- Controlled Databases showed a small mean decrease for Zypadhera-treated patients. This finding may have been driven by previous antipsychotic treatments prior to study enrolment. However, despite this small mean decrease, 20.0% of Zypadhera-treated patients with normal baseline prolactin levels and at least one postbaseline value (N=679) had abnormally high prolactin levels as seen in the analysis of abnormally high laboratory analytes in the Overall Integrated Database. Notably, a large number of patients (512 of 1478, 34.6%) had high prolactin levels at baseline, which supports the argument that this was due to previous antipsychotic treatment. Patients with high baseline prolactin levels were excluded from the analysis. The distribution of maximum postbaseline high values was further evaluated for most patients with abnormally high values postbaseline, the maximum postbaseline value was <30 µg/L (64%).

Changes in weight, prolactin, and fasting triglyceride levels were reviewed by dose in the 24-week double-blind maintenance of effect study (HGKA). Weight, prolactin, and fasting triglycerides showed significant differences in the Zypadhera doses. Patients treated with 300 mg/2 weeks Zypadhera had statistically significantly higher mean changes in prolactin and a higher incidence of high fasting triglycerides postbaseline compared with the 405 mg/4 weeks and 150 mg/2 weeks Zypadhera doses. Similarly, patients treated with 300 mg/2 weeks Zypadhera also had a statistically significantly higher mean increase in weight than patients treated with 150 mg/2 weeks Zypadhera.
Olanzapine use in general is commonly associated with metabolic adverse effects and metabolic risks associated with Zypadhera are considered to be similar than those with oral olanzapine. The applicant has been asked to reinforce the monitoring measures by emphasising these aspects in the SPC and with the RMP.

- Safety in special populations

No clinically meaningful differences were observed in any subgroup of interest with respect to TEAEs, laboratory measurements, vital signs and weight, and ECGs.

Information about intrinsic factor pharmacokinetic studies (such as renal and hepatic) has also been analyzed. Specifically, the results of the historical special population and drug interaction studies performed with olanzapine are reliable characterizations of what to expect with Zypadhera use in similar clinical circumstances. Zypadhera product should be administered to patients with the clear understanding that continuous stable treatment with olanzapine over the next few weeks to months is foreseen as clinically appropriate. Once the Zypadhera dose has been administered intramuscularly, the sustained release and absorption of olanzapine will be continuous for some time. In general, however, it is anticipated that use of Zypadhera may not be suitable for patients with clinically significant hepatic or renal impairment, especially if dosage requirements are likely to change in the near term. As a result of the intended similarities of drug exposure, currently approved labelling with regard to this special population will be useful. The SPC recommendation will be that unless a well-tolerated and effective dosage regimen using oral olanzapine has been established in such patients, Zypadhera should not be used. When switching patients using an oral dose of olanzapine less than 10 mg/day, a corresponding dose of Zypadhera should be recommended. For example, for patients using an oral dose of 5 mg olanzapine per day, a dose of 150 mg every 4 weeks is the recommended starting dose for Zypadhera.

Extrinsic factors such as alcohol or tobacco use and food habits were not specifically collected for analysis with clinical trial data. A population pharmacokinetics analysis was performed to evaluate whether gender and smoking status significantly influence olanzapine pharmacokinetics. The analysis revealed that gender and smoking status significantly influence olanzapine pharmacokinetics. Existing oral olanzapine labelling addresses safety outcomes as they relate to smoking status, as well as use with alcohol, and other central nervous system depressants. Thus, Zypadhera product labelling with respect to extrinsic factors will reflect the information, where relevant and appropriate, from currently approved labels for the oral olanzapine formulation.

- Safety related to drug-drug interactions and other interactions

Drug interaction studies have not been conducted with Zypadhera. Due to similarities in metabolism and elimination, the results of the drug interaction studies performed with oral and RAIM olanzapine are a reliable characterization of what to expect with Zypadhera in a similar situation. Consequently, the product labelling for Zypadhera will reflect the information, where relevant and appropriate, from the currently approved labels for the oral and RAIM formulations.

- Discontinuation due to adverse events

A total of 404 patients began double-blind treatment, and of these, 267 (66.1%) patients completed. The most common reasons for discontinuing the study during this period were lack of efficacy (n=59) and patient decision (n=45). There were no statistically significant differences (p=.167) across treatment groups for overall reasons for discontinuation.

Overall, the numbers of patient exposure are low to allow firm conclusions based on the safety of olanzapine pamoate formulations only. On the other hand, patient exposure to olanzapine from other olanzapine formulations is extensive. Generally, all potential or identified safety issues that have been observed based on oral olanzapine data are relevant to olanzapine pamoate as well. Potential new safety issues that would be unique to olanzapine pamoate formulation should be considered based on characteristics of this formulation and its IM dosing include the following:

- Possible local irritation at injection site
- Possible local irritation in the muscle tissue
- Possible safety issues relating to highly variable absorption of olanzapine pamoate both between patients and within a patient (under-dosing, over-dosing)
- Possibility of dose dumping
- Safety in case of inadvertent intravascular injection or injection into adipose tissue
- Possible safety issues related to pamoic acid exposure (systemic and local)
- Possibilities of absorption kinetics to be affected by variability in injection technique (e.g. injection pressure)

- Discussion on clinical safety

Overall, the safety profile of Zypadhera is consistent with the one of the oral form. Occurrence and profile of adverse events and laboratory findings are consistent with events observed in patients treated with oral olanzapine or with symptoms of the disease state.
Increase in weight and impairment of glucose and lipids metabolism are frequently reported with the use of olanzapine, and the same is expected to happen with Zypadhera. The metabolic aspect of olanzapine represents a main concern for the CHMP who therefore asked the applicant to reinforce the monitoring measures already in place. The applicant agreed to revise the SPC of Zypadhera to improve monitoring of hyperglycaemia, and weight. Instead of suggesting in the SPC a particular scheme for the baseline and follow-up monitoring of weight, glucose and lipids, it was agreed to determine, on a national basis, the most appropriate guidelines for metabolic monitoring and to provide the prescribers with a copy of these guidelines. The applicant will address this through the RMP.

However, specific aspects related to the different formulation were identified.

In particular, the IAIV events (or post-injection syndrome) deserve the utmost consideration. These events occurred in about 1.4% of the patients during the clinical development, and this figure - which is already relevant considering the controlled setting of a clinical trial – is likely to increase in the clinical practice once the product is put on the market.
The proposed methods to monitor patients after the injection (mainly based on adequate post-injection observation of the patient before and after permanence in the healthcare facility, accurate information to the patient and caregivers of possible signs and symptoms of IAIV) appear to be a reasonable measure to grant adequate safety, for the time being. When switching from oral olanzapine treatment there is a risk of post injection syndrome (IAIV event) when using Zypadhera, but it must be taken into account that there is also a decreased possibility for intentional overdose (suicidality is common in patients with schizophrenia) when compared to oral olanzapine. However, more details on future IAIV events need to be collected to further clarify and monitor the issue, and the healthcare professionals and patients should be thoroughly informed by specific programs that will be part of the RMP.

Another aspect specific for Zypadhera was represented by the treatment-emergent injection-site-related AEs. The analysis of all these events demonstrated that injection-site pain is the most common event (5.5% in the Overall Integrated Database) and that most patients reported it as “mild” in severity. It can be concluded that, injection-site pain is an expected event with the use of an IM drug and the reported incidence is not of particular concern.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

Table Summary of the risk management plan

Table 5.1. Summary of the Risk Management Plan, OP Depot

	Actions Proposed for Pharmacovigilance	Actions Proposed for Risk Minimization
Olanzapine-related safety concerns that will also apply to OP Depot		
• Weight Gain • Glucose Dysregulation • Dyslipidemia	• Continue to analyze AE reports in clinical trials • Periodically review and analyze safety database • Study F1D-MC-S014	<u>Appropriate labeling</u> • Warnings on glucose dysregulation and lipid alterations are included in Section 4.4 of the SPC. • Recommendations for monitoring of patients for glucose, lipids, and weight. • Weight gain, glucose elevation, and increases in lipids are included in the table of AEs seen in adults in Section 4.8 of the SPC. Promote awareness of appropriate metabolic monitoring by • Distributing utilized published guidelines • Referencing metabolic monitoring in the post injection syndrome Healthcare Awareness Program • Assess effectiveness of risk minimization measures (that is, Prescriber Survey and observational study [B034])

(continues)

Table 5.1. Summary of the Risk Management Plan, OP Depot (Continued)

	Actions Proposed for Pharmacovigilance	Actions Proposed for Risk Minimization
OP Depot-specific safety concerns		
Post Injection Syndrome	• Monitor AEs and SAEs: routine clinical trial and spontaneous postmarketing surveillance (routine pharmacovigilance[a]); targeted surveillance for specific AEs preidentified for targeted follow-up (targeted surveillance[b]) • Conduct a postmarketing observational study (B034) to further characterize, evaluate possible risk factors, and estimate the incidence rate of post injection syndrome in clinical practice	Appropriate labeling Provide adequate labeling to prescribers and patients about clinically relevant safety observations, including those related to post injection syndrome. Specific information and instructions to be included in the label will provide: • Description of post injection syndrome proposed as a warning in the SPC • Description of reconstitution and proper administration technique • Recommendation for a 3-hour on-site observation period post injection • Recommendation that prior to giving the injection, the HCP should determine that the patient will not travel alone to their destination • Recommendation for informing patients that for the remainder of the day of the injection, they should not drive or operate machinery, should be vigilant for signs and symptoms of a post injection syndrome event, and should be able to obtain assistance if needed • Description of the most common symptoms reported with olanzapine overdose that represent the clinical manifestation in post injection syndrome events • Recommendation for appropriate monitoring until the event resolves if an event should occur

(continues)

Table 5.1. Summary of the Risk Management Plan, OP Depot (Concluded)

	Actions Proposed for Pharmacovigilance	Actions Proposed for Risk Minimization
Post Injection Syndrome (concluded)		Risk-minimization training and communication • Product Introduction Letter sent to all psychiatrists and other targeted prescribers of depots • Provide targeted HCPs education about proper administration techniques, the risk of accidental intravascular injection with intramuscularly injected drugs, as well as the clinical presentation and management of patients reporting post injection syndrome events • Provide patients with a card containing a description of the most common symptoms associated with the post injection syndrome together with appropriate contact details and advice • Assess effectiveness of risk minimization measures (that is, annual assessment of risk-minimization training program [duration will be based on the assessment of these data and in agreement with the CHMP], an evaluation of adherence to SPC/guidelines by prescribers, and implementation of an observational study [B034])
Medication error	• Routine and targeted pharmacovigilance[a]	Prescriber education about the 2 intramuscular formulations of olanzapine, including packaging differences • Distinct packaging differences between OP Depot and RAIM

Abbreviations: AEs = adverse events; HCP = healthcare professional; OP = olanzapine pamoate; PIL = Patient Information Leaflet; RAIM = rapid-acting intramuscular; SAEs = serious adverse events; SPC = summary of product characteristics.

[a] Routine pharmacovigilance includes monitoring AE data to be in compliance with regulatory responsibilities for expedited and periodic reporting. Data are collected in a global safety database, from which signal detection and safety evaluation are performed.

[b] Targeted surveillance is based on pharmacovigilance of specific AEs preidentified for targeted follow-up.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product Zypadhera is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The nonclinical profile of olanzapine has been extensively evaluated for the oral and the rapid acting intramuscular forms. The new data provided with this submission were mainly intended for characterization of the absorption of the salt form and the possible toxicological impact due to the different extent of the exposure. Pamoic acid is also well absorbed, therefore specific studies were performed to evaluate the fate of this compound.

In rat, dog, and rabbit, OP Depot produced initial peak plasma concentrations of olanzapine and pamoate followed by a gradual decline in concentrations for up to 28 days postdose. Plasma concentrations of olanzapine following the administration of OP Depot increased with increasing dose. Plasma concentrations of pamoic acid were greater following the administration of pamoic acid alone compared to the administration of OP Depot. The plasma profiles of pamoic acid following administration of OP Depot were qualitatively similar to those obtained following administration of pamoic acid alone. The above results support the claim for a sustained release of OP Depot.
It was also concluded that pamoic acid, derived from the pamoate salt, is absorbed and rapidly excreted unchanged in nonclinical species. Injection site reaction were common.
No other specific toxicological concerns were associated with use of OP Depot in the nonclinical setting.

Efficacy

Olanzapine (oral) is an antipsychotic agent for the treatment of schizophrenia, acute manic or mixed episodes of bipolar I disorder, maintenance treatment in bipolar disorder, and agitation associated with schizophrenia and bipolar I mania. Preclinical pharmacology studies indicate that olanzapine has significant activity in dopaminergic, serotonergic, muscarinic, alpha1-adrenergic, and histaminergic systems. Olanzapine is suitable for both oral and parenteral administration. Oral (coated tablets and orodispersible tablets) and rapid-acting intramuscular (RAIM) olanzapine formulations are approved for the treatment of schizophrenia, the treatment of moderate to severe manic episodes, and the prevention of recurrence of manic episodes in patients with bipolar disorder in the European Union. The availability of new depot formulation may provide a new tool to increase patient compliance to treatment is some patients suffering from schizophrenia.

The data provided with study HGKZ, a 8-week randomized placebo controlled superiority study, showed that mean decreases in PANSS total scores compared to placebo arm from baseline to endpoint (week 8) were as follows: Zypadhera 300 mg/2 weeks: 17.81 points ($p<0.001$), Zypadhera 405 mg/4 weeks: 14.06 points ($p<0.001$), Zypadhera 210 mg/2 weeks: 13.98 points ($p<0.001$). All Zypadhera treatments were superior to placebo from week 1 visit on and continued to be more effective through-out the study period. None of the Zypadhera treatments were superior to any one of two other Zypadhera treatments over 8 weeks. Based on these findings it can be concluded that Zypadhera is superior to placebo in the treatment of schizophrenia.

The maintenance treatment study HGKA, a 24-week randomized active controlled versus oral olanzapine non inferiority study, was meant to give support to the long-term efficacy claimed by the indication. The objectives were to demonstrate non inferior efficacy of Zypadhera as compared to oral olanzapine in terms of exacerbation rates after 24 weeks, and superior efficacy of 300 mg/ 2weeks, 405 mg/4 weeks, and 15 mg/2weeks as compared to 45 mg/2 weeks (low dose close to placebo) in terms of time to exacerbation of symptoms of schizophrenia. Analysis of the first primary variable showed that Zypadhera in the pooled 2-week group analysis was no inferior to oral olanzapine (10-20 mg). However, analysis of the distribution of time to exacerbation indicated an earlier appearance of events in the Zypadhera group compared to the oral group. This is explicable due to the slow absorption of Zypadhera. Since the prescribers must be aware of the possible implications when switching from oral treatment, a recommended dosing scheme is proposed in the SPC.

Safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in table 5.1 adequately addressed these.

Overall, the safety profile of the product seems to be consistent to oral olanzapine. It is of note that the use of depot olanzapine formulation does not provide any further advantage in the overall exposure on olanzapine when compared to the use of traditional formulation. The main safety concern related to

Zypadhera compared to oral olanzapine is the possibility of the so called inadvertent intravascular injections (IAIV, term to be replaced by "Post injection syndrome"). These events have occurred in <0.1% of injections and approximately 1.4% of patients. Most of these patients have developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). In most cases, initial signs and symptoms related to this event have appeared within 1-5 hours following injection, and in all cases full recovery was reported to have occurred within 24 – 72 hours after injection.
The CHMP considers Post injection syndrome as a major safety issue, for this reason has requested the applicant to analyse all the events and submit all relevant details either during the assessment of the application and through postmarketing measures.
Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsion.
Olanzapine use in general is commonly associated with metabolic adverse effects. Metabolic risks associated with Zypadhera are considered to be similar than those with oral olanzapine. The applicant will however reinforce the monitoring measures by emphasising these aspects in the SPC and with the RMP.

- User consultation

The user test consultation provided is satisfactory.

Risk-benefit assessment

Overall benefit-risk assessment in the *maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine* is considered to be positive. When switching from oral olanzapine treatment there is a risk of post injection syndrome (IAIV event) when using Zypadhera, but it must be taken into account that there is also a decreased possibility for intentional overdose (suicidality is common in patients with schizophrenia) when compared to oral olanzapine. Risks for metabolic adverse effects do not change when switching from oral olanzapine. However, upon request of the CHMP the applicant committed to put in place measures to further improve monitoring of metabolic changes. Switching from oral olanzapine Zypadhera offers a way to increase compliance to olanzapine treatment which is a major benefit in patients that respond favourably to olanzapine but have poor compliance to the treatment.

The CHMP granted Zypadhera access to the centralised procedure under "automatic access" as a substance already approved via the centralised procedure (olanzapine), based on the assumption that the pamoate salt form does not differ from olanzapine with respect to safety and efficacy. The assessment of Zypadhera dossier confirmed that conclusion

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns

  plus

  the following additional risk minimisation activities were required: see as detailed in section 2.3

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of ZYPADHERA in the *maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine* was favourable and therefore recommended the granting of the marketing authorisation.