19 September 2013
EMA/737723/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ABILIFY MAINTENA

International non-proprietary name: ARIPIPRAZOLE

Procedure No. EMEA/H/C/002755/0000

Note

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

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List of abbreviations

Acc	Nucleus Accumbens
ADP	Action Potential Duration
AE	Adverse Event
ALT	Alanine transaminase/Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase/Aspartate Aminotransferase
AUC	Area Under Curve
BMI	Body Mass Index
CGI-I	Clinical Global Impression - Improvement Scale
CGI-SS	Clinical Global Impression – Severity of Suicide
CGI-S	Clinical Global Impression – Severity Scale
CHL	Chinese Hamster Lung
CHMP	Committee For Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Peak Plasma Concentration
CMC	Carboxymethyl Cellulose
CNS	Central Nervous System
CPK	Creatine Phosphokinqse
CYPs	Cytochromes
DA	Dopamine
DB	Double-Blind
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision
ECG	Electrocardiogram
EMA	European Medicine Agency
EPS	Extrapyramidal Symptoms
ERA	Environmental Risk Assessment
EURD	European Union reference dates
FCA	Freund's complete adjuvant
GABA	γ-aminobutyric acid
GCP	Good Clinical Practices

H	Hour(s)
HPC	Hydroxypropyl cellulose
HPLC	High pressure liquid chromatography
HPLC/MS/MS	High-performance liquid chromatography tandem mass spectroscopy
HPLC-PDA	High pressure liquid chromatography with photo-diode array detection
HR	Hazard Ratio
IM	Intramuscular
IR	Infrared
ITT	Intention To Treat
IV	Intravenous
IVRS	Centralised Interactive Voice Response System
IWB	Interactive Web Response
LOCF	Last observation carried forward
MA	Marketing Authorisation
MMRM	Mixed Model Repeated Measures
MedDRA	Medical Dictionary for Regulatory Activities
MS	Mass Spectrometry
NA	Not Available
NMDA	N-Methyl D- Aspartic Acide
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NONMEM	Non- linear mixed effects modeling methodology
OC	Observed Case
ODT	Orodispersible Tablets
PANSS	Positive and Negative Syndrome Scale
PASS	Post authorisation study
PBT	Persistent, Bioaccumulative, Toxic
PSP	Personal and Social Performance
PET	Positron Emission Tomography
PEY	Patient Exposure Years
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics

PRAC	Pharmacovigilance Risk Assessment Committee
QT	Interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle
RH	Relative Humidity
RMP	Risk Management Plan
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
US	United States
USP	United States Pharmacopeia
USSDM	Unblinded Site Study Drug Manager
vs	Versus
Vss	Steady State Volume Distribution
WBC	White Blood Cells
XPRD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Otsuka Pharmaceutical Europe Ltd submitted on 30 November 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Abilify Maintena, through the centralised procedure. As this application concerns an active substance already authorised via the centralised procedure, 'automatic' access was granted by the CHMP on 24 May 2012.

The applicant applied for the following indication: maintenance treatment of schizophrenia in adults

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application. The applicant indicated that aripiprazole was considered to be a known active substance.

The application submitted is

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).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0256/2012 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 16 December 2010. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

A new application was filed in the following country: the United States (US).

1.2. Manufacturers

Manufacturer responsible for batch release

H. Lundbeck A/S
Ottiliavej 9
DK 2500 Valby
Denmark

1.3. Steps taken for the assessment of the product

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

Rapporteur: Bruno Sepodes

Co-Rapporteur: Aikaterini Moraiti

- The application was received by the EMA on 30 November 2012.
- The procedure started on 26 December 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 March 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 March 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 11 April 2013.
- During the meeting on 25 April 2013, 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 26 April 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 June 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 11 July 2013.
- During the CHMP meeting on 25 July 2013, 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 19 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 27 August 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 5 September 2013.
- During the meeting on 16-19 September 2013, 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 Abilify Maintena on 19 September 2013.

2. Scientific discussion

2.1. Introduction

This is a complete, Article 8(3) application for Abilify Maintena (aripiprazole) for a known active substance through the centralised procedure. The product is intended for prescription only.

Aripiprazole is a novel antipsychotic. This active substance is already authorised for the treatment of schizophrenia in the European Union (EU) as tablets (5 mg, 10 mg, 15 mg, and 30 mg), orodispersible tablets (ODT) (10 mg, 15 mg and 30 mg), Oral Solution (1 mg/mL), intramuscular (IM) Solution for Injection, 7.5 mg/mL (rapid formulation). The efficacy of this atypical antipsychotic has been hypothesized to be mediated through a combination of partial agonism (agonism/antagonism) at dopamine D_2 and serotonin 5-HT_{1A} receptors as well as antagonism at serotonin 5-HT_{2A} receptors.

The claimed indication for Abilify Maintena is maintenance treatment of schizophrenia in adults.

Schizophrenia is a chronic, disabling, and progressive disease characterized by delusions, hallucinations, and cognitive impairment; symptoms and disease course differ across patients. Lifetime prevalence may vary across countries but, overall, adult schizophrenia affects 0.8 to 1% of the general population[1]. The course of schizophrenia is typically characterized by episodes of psychotic behaviours occurring at varying intervals between periods of relative symptomatic stability. Following each relapse, it is unlikely that patients will return to baseline functioning[2]. The 1-year relapse rate in schizophrenia, defined as worsening of psychopathological symptoms or rehospitalisation, is as high as 40% to 50%, and the 5-year relapse rate after a first episode is 80%[3]. Prevention of future exacerbations is a crucial goal of therapy and patients who stay on continual treatment are more likely to achieve optimal outcomes[4].

Non-adherence to treatment has been identified as a major risk factor for relapse in schizophrenia; even brief periods of non-adherence can lead to an increased risk of hospitalization and this risk increases further with worsening adherence[5]. Non adherence to treatment, ie, patients not taking their medication as prescribed, is high among patients with schizophrenia and it is estimated that approximately 50% of patients miss taking 30% or more of their medications for schizophrenia[6]. A majority of patients with schizophrenia have poor insight into the fact that they have a psychotic illness and this predisposes the individual to non-adherence with treatment and has been found to be predictive of higher relapse rates, increased number of involuntary hospital admissions, poorer psychological functioning, and a poorer course of illness[7]. Furthermore, poor insight into the illness and its consequences is thought to be one of the most important contributors to non-adherence[8]. In addition, side effects of the current medications approved for schizophrenia, such as extrapyramidal symptoms, weight gain, and cognitive impairment, also contribute to non-adherence[9].

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[1] 1) Messias E, Chen CY, Eaton WW. Epidemiology of schizophrenia: Review of findings and myths. Psychiatr Clin North Am. 2007;30:323-38; 2) McGrath J, Saha S, Chant D, Welham J. Schizophrenia: A concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30:67-76.

[2] 1) Lieberman JA, Perkins D, Belger A, Chakos M, Jarskog F, Boteva K, et al. The early stages of schizophrenia: Speculations on pathogenesis, pathophysiology, and therapeutic approaches. Biol Psychiatry. 2001;50:884-97.

[3] 1) Robinson D, Woerner MG, Alvir JMJ, Bilder R, Goldman R, Geisler S, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry. 1999;56:241-7; 2) Schennach R, Obermeier M, Meyer S, Jäger M, Schmauss M, Laux G, et al. Predictors of relapse in the year after hospital discharge among patients with schizophrenia. Psychiatr Serv. 2012;63:87-90; 3) Schooler NR. Relapse and rehospitalization: comparing oral and depot antipsychotics. J Clin Psychiatry. 2003;64(Suppl 16):14-7.

[4] 1) Peuskens J, Olivares JM, Pecenak J et al. Treatment retention with risperidone long-acting injection: 24-month results from the Electronic Schizophrenia Treatment Adherence Registry (e-STAR) in six countries. Curr Med Res Opin. 2010;26:501-9, 2) Masand PS, Roca M, Turner MS et al. Partial adherence to antipsychotic medication impacts course of illness in patients with schizophrenia: a review. Prim Care Companion J Clin Psychiatry. 2009;11:147-54.

[5] Wieden PJ, Mackell JA, McDonnell DD. Obesity as a risk factor for antipsychotic noncompliance. Schizophr Res. 2004;66:51-7; 2) Leucht S, Heres S. Epidemiology, clinical consequences, and psychosocial treatment of nonadherence in schizophrenia. J Clin Psychiatry. 2006;67(suppl 5):3-8.

[6] 1)Velligan DI, Lam YW, Glahn DC, Barrett JA, Maples NJ, Ereshefsky L, et al. Defining and assessing adherence to oral antipsychotics: a review of the literature. Schizophr Bull. 2006;32:724-42;2) Goff DC, Hill M, Freudenreich O. Strategies for improving treatment adherence in schizophrenia and schizoaffective disorder. J Clin Psychiatry. 2010;71(Suppl 2):20-6.

[7] 1)Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSMIV-TR), American Psychiatric Association, 1994.

[8] 1)Lincoln TM, Lullmann E, Rief W. Correlates and long-term consequences of poor insight in patients with schizophrenia. A Systematic Review. Schizophr Bull. 2007;33:1324-42.;2) Mutsatsa SH, Joyce EM, Hutton SB, Webb E, Gibbins H, Paul S, et al. Clinical correlates of early medication adherence: West London first episode schizophrenia study. Acta Psychiatr Scand. 2003;108:439-46.;3) Kamali M, Kelly BD, Clarke M, Browne S, Gervin M, Kinsella A, et al. A prospective evaluation of adherence to medication in first episode schizophrenia. Eur Psychiatry. 2006;21:29-33.

[9] 1)DiBonaventura M, Gabriel S, Dupclay L, Gupta S, Kim E. A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. BMC Psychiatry.

Long-acting intramuscular depot medications relieve patients from the daily need to take medication and thus have the potential to improve outcomes in the long term due to improved adherence[10]. Furthermore, regular interactions with the health care provider for injection visits can promote adherence, as failure to attend an injection visit serves as a signal for treatment non adherence[11]. Limited data comparing oral and depot formulations suggest that depot formulations may have an advantage over oral antipsychotics for relapse prevention and rates of hospitalization. After a year or more of treatment, the relapse rate in outpatients with schizophrenia treated with depot antipsychotics was significantly lower than in those treated with oral antipsychotics[12].

Currently there are two depot products approved under a centralised procedure: Zypadhera (olanzapine depot) and Xeplion (paliperidone depot) which have been authorized for the maintenance treatment of schizophrenia.

The present submission is for IM aripiprazole depot product which is a sterile, single-dose, lyophilized powder for prolonged-release injectable suspension, indented to deliver 300 mg of aripiprazole in 300-mg/vial strength and 400 mg of aripiprazole in 400-mg/vial strength. The drug product is for gluteal injection. At the initial submission, the proposed starting and maintenance dose of aripiprazole IM depot was 400 mg (2.0 mL) administered monthly by a healthcare professional as a single injection in the gluteal muscle. However, some patients may benefit from a lower maintenance dose of 300 mg (1.5 mL) based on individual patient tolerability. The first dose should be accompanied by 14 consecutive days of concurrent treatment with 10 mg to 20 mg of oral aripiprazole (or current oral antipsychotic). During the evaluation,the applicant followed the CHMP recommendation to change the indication to the following: “maintenance treatment of schizophrenia in adult patients stabilized with oral aripiprazole”. The posology was consequently amended to remove the reference to concomitant treatment with current other antipsychotic.

2.2. Quality aspects

2.2.1. Introduction

Abilify Maintena is presented as powder and solvent for prolonged-release suspension for injection. Two strengths have been developed; 300 mg and 400 mg. The powder vial contains a sterile lyophilized cake, which is to be reconstituted with 1.5 or 1.9 ml water for injections from the solvent vial, to obtain an extended-release injectable (IM) suspension, containing 200mg/mlaripiprazole (as monohydrate) as active substance. Abilify Maintena is available in two pack sizes. The package contains powder and solvent vials, syringes, a vial adapter, and needles necessary for the reconstitution and administration.

2012;12:20;2) Ascher-Svanum H, Zhu B, Faries D, Lacro JP, Dolder CR. A prospective study of risk factors for nonadherence with antipsychotic medication in the treatment of schizophrenia. J Clin Psychiatry. 2006;67:1114-23.

[10] 1)Weiss KA, Smith TE, Hull JW, Piper AC, Huppert JD. Predictors of risk of nonadherence in outpatients with schizophrenia and other psychotic disorders. Schizophr Bull. 2002;28:341; 2) Lang K, Meyers JL, Korn JR, Lee S, Sikirica M, Crivera C, et al. Medication adherence and hospitalization among patients with schizophrenia treated with antipsychotics. Psychiatr Serv. 2010;61:1239-47;3)Kane JM. Review of treatments that can ameliorate nonadherence in patients with schizophrenia. J Clin Psychiatry. 2006;67(suppl 5):9-14.

[11] 1) Lindenmayer JP. Long-acting injectable antipsychotics: focus on olanzapine pamoate. Neuropsychiatr Dis Treat. 2010;6:261-7.

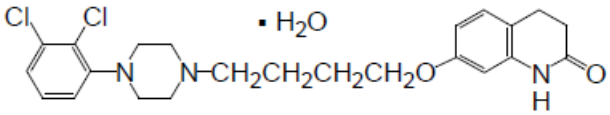
[12] 1)Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry. Epub 01 Mar 2011;2)Grimaldi Bensourda L, Rouillon F, Astruc B, Rossignol M, Benichou J, Falissard B, et al. Does long-acting injectable risperidone make a difference to the real-life treatment of schizophrenia? Results of the Cohort for the General study of Schizophrenia (CGS).Schizophr Res. 2012;134:187-94;3) Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia - a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res. 2011;127:83-92.

The powder vial contains the following excipients: carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, and sodium hydroxide. The solvent vial contains water for injections. The list of excipients is described in section 6.1 of the SmPC.

2.2.2. Active Substance

Aripiprazole monohydrate is a white to off-white crystal. It is not hygroscopic, and is very soluble in acetic acid, freely soluble in benzyl alcohol and tetrahydrofuran, soluble in dimethyl sulfoxide, slightly soluble in ethanol and acetonitrile, and insoluble in methanol. It is practically insoluble in water and shows a profile characteristic of basic organic compound. The solubility increases with a decrease of pH. The chemical name is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril, as monohydrate (1:1).

Aripiprazole monohydrate has the following structural formula:



Aripiprazole exists in several crystalline forms. The monohydrate is the most stable crystal form in water. Aripiprazole has no asymmetric centres and is not optically active. There is no Ph.Eur. monograph for aripiprazole.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. The chemical structure of aripiprazole monohydrate is confirmed by elemental analysis, spectral analysis (UV, IR, NMR, MS), single crystal X-ray analysis and thermal analyses (DTA and TGA). The monohydrate form is confirmed by single crystal structure analysis.

Manufacture

Sterile aripiprazole monohydrate active substance is obtained from two suppliers. One of the suppliers has provided the information on the active substance in the form of an active substance master file (ASMF).

Sterile aripiprazole monohydrate is manufactured aseptically by recrystallization of aripiprazole. Aripiprazole anhydrous is the active substance of Abilify, a medicinal product from the same applicant. The sterile crystallization is a one step process with no intermediates involved. The manufacturing of sterile aripiprazole monohydrate includes: i) synthesis of aripiprazole followed by ii) dissolution, iii) sterilization by filtration, iv) aseptic recrystallisation, v) aseptic drying and vi) aseptic packaging. Since this is an aseptic process, the only in-process control that is performed is the bioburden test before sterilisation by filtration, which is acceptable. No reprocessing is proposed. The manufacturing process is well described and the use of sterilisation by filtration instead of by heat has been adequately justified (see also the section on pharmaceutical development). Impurity profiles before and after the sterile crystallization show that no new drug-related impurities are generated by the recrystallization process.The manufacturing process has been appropriately validated.

Specification

The active substance specifications for both suppliers include tests for: description, identity (IR and XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), heavy metals (USP), residue on ignition (USP), bacterial endotoxins(USP/Ph.Eur.) and sterility (USP/Ph.Eur.).

The critical quality attributes for sterile aripiprazole monohydrate are crystalline form and sterility, which are adequately controlled by the manufacturing process and specifications. Batch analysis data for 21 representative batches of sterile aripiprazole monohydrate drug substance used in pre-clinical, clinical, and stability studies, were presented by the applicant. Batch analysis data cover both suppliers and demonstrate that all batches comply with the proposed specifications and that the active substance can be manufactured reproducibly.

Stability

The ICH formal stability studies were performed on three commercial-scale batches of sterile aripiprazole monohydrate active substance, manufactured at both active substance manufacturers and packaged in the proposed commercial primary packaging and closure system. The long-term stability study samples were stored at 30°C/65% RH and the accelerated storage conditions were 40°C/75% RH. Up to 36 months long-term data and up to 6 months accelerated stability data have been provided. Stress stability studies were carried out on one batch. The samples were tested at 25°C/90% RH (open dish), 40°C/75% RH (open dish), 50°C, and under white fluorescent/near ultraviolet lamps. The following parameters were tested: description, identification (IR and XRPD), impurities (HPLC), water content (KF), assay (HPLC), sterility, and bacterial endotoxins. The analytical methods used were adequate for stability determination of the substance.
The results of a photostability study indicate that the drug substance is stable to light. The data from the open-dish studies and an elevated temperature study (50°C) demonstrate the stability of the drug substance to heat and humidity. The stability results indicate that the drug substance manufactured by the proposed suppliers is stable and justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The aim was to develop a prolonged-release formulation for intramuscular injection that prevents the relapse of schizophrenia by maintaining the effect for 4 weeks after one single injection. Because an administration volume of not more than 2 ml is preferable for intramuscular injections, the concentration of the formulation to be developed was defined as 200 mg/ml. To keep irritation at the administration site acceptable and to reduce pain on administration, it is important that the finished product can be injected with a 21G or thinner needle.

Aripiprazole monohydrate is very poorly soluble in water in the physiological pH range, and thus, the absorption rate of aripiprazole from the intramuscular injection site is dependent on the dissolution rate of the suspended crystalline particles of aripiprazole monohydrate. The dissolution rate is considered to be mainly influenced by the mean particle size and crystalline form. During the development, the influence of the crystalline form on the pharmacokinetic profile in rats was studied.

In view of the importance of the crystalline form and particle size for the absorption rate, the applicant developed an appropriate dissolution method, which was able to detect any differences in the particle size distribution (mean particle size) and different crystalline forms, which may vary during the manufacturing process and influence the *in vivo* pharmacokinetic profiles of the formulation in animals. The dissolution test method was demonstrated to be reproducible and is routinely carried out during the drug product release testing.

The excipients in Abilify Maintena are commonly used in injectable dosage forms and their quality is compliant with Ph. Eur standards. The compatibility of the drug substance and the excipients has been studied. The excipients in the powder vial are: carmellose sodium (suspending agent), mannitol (bulking agent), sodium dihydrogen phosphate monohydrate (buffering agent), sodium hydroxide (pH adjustment agent), and nitrogen. For sodium dihydrogen phosphate monohydrate adequate in-house specifications have been proposed. The solvent vial contains only water for injections (vehicle for reconstitution). There are no novel excipients used in the finished product formulation. The list of excipients can be found in section 6.1 of the SmPC.

The pharmaceutical development focussed on i) selecting a delivery system, ii) selecting the appropriate suspension, and iii) controlling the mean particle size and crystal form.

Based on *in vivo* drug release studies in rats and local tolerance studies in rabbits, a flocculated suspension was chosen as the starting point for further development because it was shown to be the most promising in meeting the initial target product profile. However, a deflocculated suspension showed lower irritation at the administration site compared with the flocculated suspension.

Because particle sedimentation occurred when the deflocculated suspension was stored for a long time, resulting in a difficult re-dispersion, it was decided to select, as the final drug product, a homogenised, deflocculated lyophilised formulation, which has to be reconstituted with sterile water for injections immediately prior to injection. The applicant demonstrated that the resulting suspension is easy to reconstitute, is homogeneous, has no aggregated masses (coarse particles), and exhibits excellent syringeability. The same formulation has been used throughout the clinical trials.

The manufacturing process development focused on finding an appropriate way to obtain a sterile medicinal product. Studies demonstrated that the drug substance is not suitable for terminal sterilization. Aripiprazole monohydrate is discoloured and slightly decomposed by both gamma-ray and electron beam, and is melted by dry heat sterilisation. Aripiprazole monohydrate particles in aqueous suspension tend to agglomerate by steam heat sterilisation. Based on these findings, aseptic processing, instead of terminal sterilisation, had to be employed for the manufacturing process of Abilify Maintena. The manufacturing process of the commercial product is the same as the one used for the batches in the Phase 3 clinical trials.

Abilify Maintena is presented as a carton box containing one vial each for powder and solvent, a sterile syringe with pre-attached needle for reconstitution, a sterile syringe for administration, two hypodermic safety needles, and a vial adapter. The powder and solvent vials are Type-I glass vials, which are closed with a laminated rubber stopper, and sealed with a flip-off aluminium cap. This type of container closure system is commonly used for injectable dosage forms and is adequate to support the stability and use of the product. All materials comply with applicable European regulations, and declarations of EC conformity have been provided for the syringes, needles, and the vial adapter.

Adventitious agents

No excipients of animal or human origin have been used.

Manufacture of the product

Abilify Maintena is a lyophilised product, produced by aseptic processing. The process is considered to be a non-standard manufacturing process.

The manufacturing process of the powder vials consists of the following steps: i) sterile filtration of the vehicle solution, ii) addition of the sterile drug substance aseptically, iii) milling and filtration to obtain the desired particle size, iv) filling the suspension into depyrogenated vials and partially stoppering the filled vials, v) lyophilisation, and subsequently vi) stoppering and capping with steam sterilised aluminum caps.

The vehicle solution is the solution in which the following excipients are dissolved during the drug product manufacturing process: carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, and sodium hydroxide and water for injections. Because the viscosity of carmellose sodium is known to be irreversibly affected at high temperatures when in aqueous solution, sterile filtration was selected for the sterilization method of vehicle solution instead of heat sterilisation.. Although the EU GMP guideline recommends the use of heat sterilization, the use of sterile filtration was accepted for the reasons described above.

In-process overfill is in place to compensate for loss of aripiprazole monohydrate due to adhesion of the drug substance to the filling lines. Overfill is also needed to compensate for the fact that after reconstitution some suspension cannot be withdrawn from the vial due to adhesion to the vial wall. The critical manufacturing steps (milling and lyophilisation), critical process parameters and control strategy have been adequately described and justified.

The manufacturing process of the solvent vials consists of: i) washing, drying, sterilising, and depyrogenation of the vials, ii) filtration of the water for injections, iii) filling, and iv) stoppering. Water for injections is generated from highly purified water by distillation. Highly purified water is generated from potable water by reverse osmosis coupled with filtration and deionization. The quality complies with the Ph.Eur. and US Pharmacopoeia (USP) monographs. The details of the manufacturing process, flow diagrams and in-process controls are provided. There are no critical steps in the manufacture of the sterile water for injections vials.

The manufacturing process has been fully validated for three batches of each strength of the powder vials and three batches of the solvent vials. The validation results demonstrate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications of the powder vial include appropriate tests for description, identity (HPLC-PDA and XRPD (Ph.Eur.)), bacterial endotoxins (Ph.Eur.), sterility (Ph.Eur.), content uniformity (Ph.Eur.), pH (Ph.Eur.), water content (Ph.Eur.), syringeability, dissolution (Ph.Eur.), polymorphs (XRPD (Ph.Eur.)), particle size distribution (laser light diffraction, Ph.Eur.), aggregates (particle image analyzer), impurities/degradation products (HPLC) and assay (HPLC).

The release specifications of sterilised water for injections are as in the monograph of the Ph.Eur.

Batch analysis data have been provided for six production scale batches of both strengths of the powder vials and for three validation batches of the water for injections vials. The data confirm the consistency of the manufacturing process and its ability to manufacture the finished product with the intended product specification.

Stability of the product

The stability studies were carried out on twelve production-scale batches, i.e. on six batches of each strength. Up to 24 months data have been presented for batches stored at 5ºC, 25ºC/60%RH and 30ºC/75%RH and up to 6 months data are available for batches stored at 40ºC/75%RH. The batches were packed into the packaging materials, which are intended for marketing.

The stability samples have been tested for: description, identification (by HPLC-PDA and XRPD), bacterial endotoxin, sterility, content uniformity, pH, water content, particulate matter, syringeability, dissolution, limit test for polymorph particle size distribution, aggregates (by particle image analyzer), impurities/degradation products and assay.

The absence of stability studies on powder samples stored in the inverted position has been justified based on the fact that the solid cake does not come into contact with the stopper when placed in inverted position. Additional tests that have been performed are: checking the maximum injection force, suspension viscosity, amorphous limit test (by thermal analysis and XRPD), anhydrous crystalline form (by NMR), crystalline form (by XRPD), osmolarity ratio, seal integrity test, insoluble foreign matter, dissolution and pressure in container.

Stress stability studies have been performed on one commercial-scale batch of each strength of the powder vials. The studies were performed under the following conditions: 3 months at 50ºC, exposure to fluorescent light and UV for 600 hours and freeze-thaw cycling (-20ºC to 40ºC/ Day) for 2 weeks. In addition, a low humidity study (at 40ºC/20%RH) has been performed on one commercial-scale batch of each strength of the powder vials and an in-use stability study was conducted on the reconstituted suspension. Information on the in-use stability has been included in section 6.3 of the SmPC.

Based on available stability data, the proposed shelf-life as stated in the SmPC is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were no unresolved quality issues having an impact on the benefit/risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non clinical data mainly consisted of studies previously conducted with aripiprazole as oral or IM rapid solution for injection and used in support of the granted marketing authorisation for these formulations (Abilify). Furthermore, specific studies were performed with the IM aripiprazole depot to further characterise the pharmacokinetic and toxicological profiles of the formulation applied for and are presented in this application.

2.3.2. Pharmacology

No specific pharmacology studies in animal models for IM aripiprazole depot have been conducted taking into account existing pharmacological data for oral aripiprazole and its metabolites.

The pharmacological properties of aripiprazole are mediated through a combination of partial agonism at dopamine D2 and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2A receptors as described below.

Primary pharmacodynamic studies

Aripiprazole (OPC-14597, OPC-31, BMS-337039) binds with high affinity to dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors, with moderate affinity to dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, α_1-adrenergic, histamine H_1 receptors and the serotonin reuptake site. Aripiprazole exhibits low affinity for muscarinic receptors.

Aripiprazole potently activates recombinant human D_2 receptors which are coupled to the inhibition of cAMP accumulation achieving a maximal effect of approximately 80% of that produced by the endogenous agonist dopamine and in cultured rat anterior pituitary cells, it produces a dose-dependent inhibition of prolactin release with a maximal inhibitory effect of 70% of that displayed by dopamine. The affinity of aripiprazole for rat 5-HT_{2A} receptors is lower than that of risperidone and chlorpromazine but is comparable to that of haloperidol and clozapine. Additionally, aripiprazole inhibits 5-HT_{2A}-mediated behaviours, suggesting 5-HT_{2A} antagonist activity. Aripiprazole also inhibits gamma-butyrolactone and reserpine-induced increases in 3, 4-dihydroxyphenylalanine (DOPA) accumulation consistent with a reduction in presynaptic tyrosine hydroxylase activity, and this effect was blocked by the D_2 receptor antagonist haloperidol and produces a hyperpolarization of ventral tegmental area dopamine neurons accompanied by a concomitant decrease in firing produced by activation of D_2 auto-receptors, an effect which was antagonized by the D_2 receptor antagonist domperidone.

Aripiprazole has cataleptogenic effects in rodents. In mice, the ratio of doses that are cataleptogenic to those that inhibit apomorphine-induced stereotyped behaviour was about 11 times that of chlorpromazine and 5 times that of haloperidol. In rats, the dose ratio of aripiprazole was about 14 times that of chlorpromazine and 8 times that of haloperidol. Aripiprazole was 4.8- and 7.1-fold less potent than olanzapine and risperidone, respectively in inducing catalepsy.

In electrophysiologic studies, the effects of aripiprazole on neuronal activity in nucleus accumbens neurons, activated monosynaptically by stimulation of the parafascicular nucleus of the thalamus, were examined. Although aripiprazole alone was without effect, dopamine-, SKF 38393- and quinpirole-induced inhibition of spike generation in Acc neurons tended to be antagonized during simultaneous application of aripiprazole. Aripiprazole, as well as domperidone, a selective D_2 receptor antagonist,

show significant inhibition of striatal neuronal firing elicited by stimulation of dopaminergic inputs from the substantia nigra. Aripiprazole also blocks quinpirole-induced firing in striatal neurons, but does not alter glutamate-induced firing, suggesting that aripiprazole blocks dopamine D_2 receptors on striatal cells receiving dopaminergic input from the substantia nigra. Aripiprazole produces a reduction in the firing rate of serotonin-containing dorsal raphe neurons in rats which is reversed by administration of the selective 5-HT_{1A} antagonist WAY-100635. Additionally, in acutely dissociated hippocampal pyramidal neurons of the rat, aripiprazole (at 10^{-5}M) significantly reduces the γ-aminobutyric acid (GABA)-induced inward current but is less potent than the neuroleptic, zotepine. Aripiprazole does not influence the N-methyl-D-aspartic acid (NMDA)-induced current.

In behaviorial studies, aripiprazole showed a significant inhibition of the conditioned avoidance response comparable to conventional antipsychotics (e.g. haloperidol, chlorpromazine) and demonstrated anti-conflict behaviour in rats like the atypical antipsychotic clozapine.

Secondary pharmacodynamic studies

Aripiprazole produced a dose-dependent reduction in body temperature in both mice ($\geq$ 50 mg/kg/day) and rats ($\geq$ 100 mg/kg/day). Such hypothermic effects are consistent with the actions of serotonin 5-HT_{1A} agonists, including partial agonists in both rodents and humans. In comparison, haloperidol resulted in a slight reduction in body temperature of mice at an oral dose 30 mg/kg and reduced body temperature at oral doses 100 mg/kg or higher in rats.

Safety pharmacology programme

Central and peripheral nervous systems

Aripiprazole was less potent than chlorpromazine and haloperidol in producing behavioral signs consistent with CNS depression, in inducing catalepsy, and in suppressing spontaneous motor activity and, unlike these comparators, did not cause convulsions. Additionally, it reduced motor coordination and prolonged the duration of hexobarbital-induced hypnosis with a potency comparable to chlorpromazine. In contrast, aripiprazole demonstrated less potential than chlorpromazine or haloperidol to induce muscular relaxation and analgesia.

Cardiorespiratory system

Aripiprazole and OPC-14857 inhibited the HERG/Ikr current only at very high multiples of the maximum steady-state plasma free-drug concentration and there were no effects on action potential duration (APD) in the rabbit Purkinje fiber assay. OPC-3373 demonstrated no in vitro inhibition of HERG/Ikr current or prolongation of APD at concentrations up to 10 μM. Neither aripiprazole nor the main human metabolites (OPC-14857, OPC-3373) accumulate in rat cardiac tissue following single or repeat (13 days) dosing. Potential cardiovascular effects were also assessed in in vitro and in vivo safety pharmacology studies (anesthetized dogs) and in toxicology studies (39 week treatment in monkeys) where no significant changes were observed. Furthermore, there is no evidence of drug-related QTc (Bazett's correction) interval prolongation or other clinically significant ECG abnormalities in over 2100 patients treated with aripiprazole.

Other systems and tissues

In vitro and in vivo safety pharmacology studies were conducted to assess the potential of aripiprazole to alter gastric secretion, gastrointestinal motility, smooth muscle contractility, and urine volume and electrolyte excretion. These studies indicated that aripiprazole has little potential to cause gastrointestinal or renal side effects or affect smooth muscle contractility.

Pharmacodynamic drug interactions

Co-administration of D2 receptor antagonists such as chlorpromazine with aripiprazole reduce the presynaptic dopamine (DA) autoreceptor agonist efficacy of aripiprazole. In contrast, lorazepam alone significantly reduces DOPA accumulation following reserpine injection and significantly enhances aripiprazole's action as a presynaptic DA autoreceptor agonist. Fluoxetine did not alter aripiprazole's actions on presynaptic DA autoreceptors. Co-administration of aripiprazole with other agents that produce postsynaptic D2 receptor blockade (haloperidol, chlorpromazine, risperidone) act in an additive manner to block DA-mediated behavior and induce catalepsy. Concomitant administration of aripiprazole with haloperidol or risperidone produced a greater increase in plasma prolactin levels in rats than did aripiprazole alone. However, combined administration of aripiprazole with chlorpromazine did not produce such an increase. Concomitant administration of aripiprazole with lorazepam decreased plasma prolactin levels. However, lorazepam alone significantly reduced prolactin levels. In contrast, co-administration of aripiprazole with benztropine or fluoxetine had little effect on plasma prolactin levels. Similar to the effects on DA-mediated behaviour, co-administration of aripiprazole with D2 receptor antagonists enhanced blockade of pituitary D2 receptors culminating in increased prolactin levels.

2.3.3. Pharmacokinetics

In addition to the existing pharmacokinetic data supporting the granted marketing authorisation (MA) for the oral and IM rapid aripiprazole (Abilify), the pharmacokinetic profile of IM aripiprazole depot and its metabolites was studied in rats.

No specific studies on plasma protein binding and distribution to blood cells were conducted, nor excretion studies or studies on placenta transfer. Available studies are derived from oral aripiprazole or IM rapid aripiprazole.

The pharmacokinetics of aripiprazole was dose linear and qualitatively similar in mice, dogs, monkeys, and humans; however, dose-dependent bioavailability was seen in rats likely due to saturation of the presystemic metabolism and/or elimination. The absolute oral bioavailability of aripiprazole was 47% in mice, 16% at 10 mg/kg in rats, 6-12 % in dogs, 8% in monkeys, and 87% in humans. In bile duct-cannulated rats, aripiprazole was well and rapidly absorbed from the gastrointestinal tract and about 80% of drug-related material was recovered in the bile, suggesting that the low oral bioavailability in rats was due to extensive presystemic metabolism.

The steady-state volume of distribution (Vss) of aripiprazole in animals and humans was substantially greater than the volume of total body water, suggesting extensive extravascular distribution of the drug and/or preferential binding to tissue proteins. Aripiprazole readily crosses the blood-brain barrier, as there is rapid uptake and extensive distribution of aripiprazole in the rat brain following its oral administration. Aripiprazole was extensively serum protein bound and the binding site was determined to be albumin site II specific. The *ex vivo* protein binding of aripiprazole was 99.75% and was similar to the protein binding determined by equilibrium dialysis *in vitro.*

Following [14C]-aripiprazole administration to pregnant rats, drug-related radioactivity was widely distributed in maternal tissues. Distribution of radioactivity to the fetus was low and only a trace amount of radioactivity was detected in the amniotic fluid even though concentrations of radioactivity in the placenta were 1.3-4.5 times higher than that in maternal plasma. Highest fetal tissues concentrations were observed in the fetal liver; lower concentrations were noted in fetal kidney, heart, blood, lung, and brain. Drug-derived radioactivity was secreted in the milk within 0.5 h after oral administration of [14C]-aripiprazole to lactating rats. In addition, the milk vs. blood concentration ratios were greater than one for up to 24 h postdose. These results in rats suggest there is a potential

for fetal and neonatal exposure to aripiprazole if administered to pregnant or lactating women. This information is included in section 4.6 of the SmPC.

Following injection of aripiprazole IM depot formulation in rats, the Cmax and AUC of aripiprazole in the males increased with the dose increment. Aripiprazole injected as a depot formulation remained at the injection site without being metabolized or decomposed for a long time. There was no significant sex difference observed in the blood concentration profiles in the rats administered at 3.75 mg/kg. After 14C-aripiprazole IM rapid formulation was injected to male rats in single IM administration of 3.75 mg/kg, the radioactive concentrations in blood, cerebrum, cerebellum, eyeball, lung, liver, adrenal gland, kidney, muscle and plasma were the highest at 0.25 hours after the administration and decreased thereafter. At 168 hours, the radioactive concentrations in harderian gland, sub-maxillary gland, liver, adrenal gland and kidney were detected, however, the radioactivity in the other tissues (blood, cerebrum, cerebellum, eyeball, lung, fat, muscle and plasma) was not detected. The residual radioactivity of the femoral muscle injected with the test article at 0.25 hours was 35.24% of dose. The residual radioactivity in the injection site (muscle) at 168 hours was 0.68% of dose. This result showed that almost all dosed radioactivity from the femoral muscle injected with the test article was eliminated by 168 hours.

Aripiprazole was completely bioavailable following IM and SC administration. No new metabolites are formed following IM administration of aripiprazole. There was no sex difference in the plasma concentrations of aripiprazole metabolites after dosing of aripiprazole IM depot formulation. The rank order of the Cmax and AUCt for aripiprazole and its metabolites was aripiprazole > DM-1451 > OPC-3373 > OPC-14857.

After 14C-aripiprazole IM rapid formulation was injected to both male and female rats in single IM administration of 3.75 mg/kg, the cumulative urinary and fecal excretion rates of radioactivity within 168 hours after the administration were 4.88% and 92.05% in the male rats, and 6.57% and 91.09% in the female rats, respectively.

2.3.4. Toxicology

The following toxicology studies were performed with IM aripiprazole depot: 1) single dose toxicity studies in dogs, 2) repeat-dose toxicity studies up to 6 months in rats, 12 months in dogs, and 4 weeks in monkeys and 3) local tolerance studies in several species (rats, rabbits, dogs and monkeys).

Because the plasma concentration of aripiprazole after IM administration in humans does not exceed those after oral administration, existing data for oral carcinogenicity and reproductive toxicity testing of aripiprazole as described below, were considered sufficient to support the present application. In addition, the genotoxic potential of aripiprazole and its metabolites have been adequately evaluated in the battery of genotoxicity tests previously conducted in support of the granted marketing authorisation of the oral and IM rapid aripiprazole (Abilify) and no additional studies were considered necessary. Available genotoxicity results are presented below.

Single dose toxicity

Following single IM administration of aripiprazole to dogs (doses up to 400 mg), swelling of injection sites was noted on Days 1 to 4 at 100 mg in females and at doses of 200 and 400 mg in males and females. Microscopically, a dose-related, minimal to moderate granulomatous inflammation was observed. The inflammatory response was characterized by the presence of numerous epithelioid macrophages with lesser numbers of multinucleated (foreign body) giant cells and lymphocytes that were localized primarily in the interstitial tissue of skeletal muscle. The macrophages were associated with deposits of birefringent crystalline material, interpreted as test article, and represented a foreign

body reaction to deposited drug. Injection site alterations were slightly diminished in size and severity on Day 43 (study termination) compared to Day 29. The inflammation and deposited drug at the injection sites decreased slightly over time, but did not completely resolve after 6 weeks. There was no evidence of drug-related skeletal muscle injury or fibrosis/fibroplasia at the injection sites.

Tremors were observed at all doses with decreased activity observed in males and females at ≥200 mg on the day of dosing but were not present the next day (Day 2). These effects were considered related to the exaggerated pharmacological activity of aripiprazole. Other clinical observations included pain/discomfort at the injection site, hind limb lameness/limping (all doses) and hind limb muscle fasciculations in 1 male at 300 mg and 1 female at 400 mg. Lameness/limping occurred on the day of dosing and resolved by Day 2. Muscle fasciculations were noted on Day 2 and resolved by Day 3. Drug-related changes consisted of increased white blood cell counts, neutrophil counts and fibrinogen levels in all treated male and female groups on Day 2. Minimal decreases in serum potassium occurred in all treated male and female groups on Day 2.

Repeat dose toxicity

Preliminary data in rats (50 or 100 mg/kg/day, weekly or biweekly injection) and dogs (20 or 40 mg/kg/day, weekly (1 or 2 injections) or biweekly injection) revealed injection site tissue reactions. At necropsy, white (discolored) foci were observed in the injection sites of all rats and dogs treated with the aripiprazole suspension. In dogs, the foci were characterized microscopically by slight granulomatous inflammation. A scab in the injection site was also observed for only 2 days following the second injection in one dog treated biweekly with 40 mg/kg/day. In monkeys, following 2 week administration of once daily injection of 2, 4 or 7.5 mg/kg/day, dose-related, increased incidences of tremors and hypoactivity were observed in males and females with the onset generally occurring within 1 to 2 hours post-dose and resolving by 8 to 24 hours post-dose. At 7.5 mg/kg/day, increases were observed in reticulocyte counts and ALT levels in males and females and AST levels in females. Also, urine pH was minimally increased in males. Red discoloration at the injection site was noted across all groups. Microscopic findings at the injection sites included degeneration, necrosis and regeneration of the muscle and sub-acute inflammation, hemorrhage, edema, and fibroplasia/fibrosis of the muscle and adjacent connective tissue. Minimal hemorrhage at the injection site was seen in all groups and varied from minimal (2 and 4 mg/kg/day) to mild severity (7.5 mg/kg/day). At the end of the 2-week post-dose period, all drug-related changes recovered with nearly complete reversibility of injection site changes.

In rats, at doses of 25, 50, or 100 mg/kg administered weekly for 26 weeks, body weights and food consumption of high-dose rats were generally lower than controls during the study with the decrease observed more in males than females. During recovery, the body weights of male rats at the high dose remained lower than controls. Transient changes in body weights and food consumption were observed at 50 mg/kg. Subcutaneous nodules and swelling (raised area) at the injection sites in the animals at all doses of aripiprazole with a greater incidence of these signs at the high dose. The subcutaneous nodule and swelling were occasionally observed after injection, but resolved either between injections or as the study progressed. At necropsy, development of the mammary gland was observed in the females given 25 mg/kg and was higher at the end of the dosing period, and was also noted in the females given 100 mg/kg at the end of the recovery period. The morphological changes in the reproductive and mammary tissues in the females given 25 mg/kg and higher and atrophy of pars intermedia in the pituitary gland in the males and females given 25 mg/kg and higher were considered pharmacologically mediated and a consequence of D_2 partial agonistic activity of aripiprazole. Decreased liver weights in the males and decreased adrenal and relative uterine weights in females

given 100 mg/kg/day were observed at the end of the dosing phase. Increased spleen weights were observed in females treated with 100 mg/kg.

In dogs, at doses of 10, 20, or 40 mg administered weekly for 26 weeks, a subcutaneous nodule (raised area) at the injection site in the animals given 20 and 40 mg/kg was noted. This subcutaneous nodule was occasionally observed after injection, but resolved over time. For all treated animals, the white foci observed at the injection site were characterized microscopically by slight granulomatous inflammation at the end of the dosing and recovery periods in line with the observations made for the single-dose toxicity study. In another study using the same doses but of longer duration (52 weeks), no drug-related deaths occurred throughout the dosing period although 1 control female receiving physiological saline was euthanized at Week 51 due to sudden deterioration associated with heart failure. Necrosis of muscle fibers was noted in one female given 40 mg/kg at the end of the 52-week dosing period and was limited to the area of granulomatous inflammation. This was considered a consequence of focal ischemia secondary to granulomatous inflammation since interstitial tissues including vessels in the necrotic muscles were also necrotic. No evidence of muscle necrosis at the injection site was observed in any other treated animals. Also, no other drug-related gross or microscopic changes were noted in the treated dogs. At the end of the 26-week recovery period, there were no gross or histopathological changes at the injection site in any animals given 40 mg/kg.

In monkeys, at doses of 2, 4, or 7.5 mg/kg/day, administered as daily injection for 4 weeks, a dose-related pharmacologically mediated decreased activity and tremors were evident at all doses in line with the observation made for the single-dose toxicity study. Decreased food consumption, which was likely secondary to the pharmacologic activity of aripiprazole, occurred in all drug-treated animals except for 2 males at 2 mg/kg/day. During the dosing phase, mean food consumption of males given 2, 4, or 7.5 mg/kg/day was about 24%, 63%, and 51% lower than control, respectively. Corresponding values in the females given 2, 4, or 7.5 mg/kg/day were about 34%, 62%, and 58% lower than control, respectively. Dehydration and a thin appearance of monkeys in the 4 and 7.5 mg/kg/day groups also were observed and were considered related to the reduced food consumption. Dose-related clinical findings at the injection sites included an increased incidence of scabbing at all doses and red discoloration at 7.5 mg/kg/day. Minimal increases in serum AST levels at 4 or 7.5 mg/kg/day were attributed to minor skeletal muscle injury at injection sites.

Genotoxicity

Aripiprazole demonstrated genotoxic potential in several tests: (1) in the bacterial reverse-mutation test where a slight concentration-dependent increase of reverse mutations in TA100 strain in the presence of S9 metabolic activation was noted, (2) in the in vitro chromosomal aberration test (CHL) at 30 μg/ml and above, corresponding to highly cytotoxic concentration and suggesting an indirect clastogenic effect, and (3) in the oral in vivo micronucleus tests in mice at 100 mg/kg and above, possibly related to a profound drug-induced hypothermia. Aripiprazole demonstrated no genotoxic potential in the bacterial DNA repair assay, forward gene mutation test in mouse lymphoma cells, and in vivo-in vitro unscheduled DNA repair assay in rat hepatocytes. Based on the weight of evidence from the battery of genotoxicity studies, aripiprazole is not considered to pose a genotoxic risk to humans at therapeutic doses and exposures.

Carcinogenicity

In mice, dietary administration of aripiprazole at doses of 1, 3, and 10 mg/kg/day for 104 weeks was associated with increased incidences of mammary tumors, namely adenocarcinomas /adenoacanthomas and pituitary adenomas in females at the mid- and high doses. Gall bladder adenoma was observed in both sexes at the two highest doses, but not in control or the lower dose

tested. A dose-related increase of skin schwannoma or malignant schwannoma as well as spleen hemangioma or hemangiosarcoma was also observed. The incidence of liver hemangioma/hemangiosarcoma and hepatoblastoma was increased in males (an effect not observed in females) comparatively to control for all tested doses. Increases in mammary and pituitary neoplasms as well as other drug-related mammary/reproductive tissue alterations in females were considered, by the applicant, likely to be secondary to aripiprazole-related increases in serum prolactin.

In a supplementary study, dietary administration of aripiprazole at a dose of 30 mg/kg/day to mice for 100 to 104 weeks was associated with increased incidences of mammary adenocarcinomas/ adenoacanthomas and pituitary adenomas in female mice. Increases in mammary and pituitary neoplasms, as well as other drug-related mammary/reproductive tissue alterations in female mice were considered to be secondary to aripiprazole-related increases in serum prolactin. An increased incidence of liver haemangioma or hemangiosarcoma was also observed.

In rats, dietary administration of aripiprazole at doses of 1, 3, and 10 mg/kg/day to F344 rats for 104 weeks was associated with an increased incidence of mammary gland fibroadenoma (a benign tumor) in females at the high dose only. The mammary fibroadenomas and uterine atrophy were considered, by the applicant, to be secondary to aripiprazole-related increases in serum prolactin. There was no drug-related increased incidence of tumors in male rats.

In order to reach a maximum tolerated dose, another oral carcinogenicity study was conducted using gavage administration to Sprague Dawley rats at doses of 10, 20, 40, or 60 mg/kg/day for 104 weeks. In this study, there was an increased incidence of adrenocortical tumors (adenomas and carcinomas) at 60 mg/kg/day in females only. Drug-related non-neoplastic findings at 40 and 60 mg/kg/day included increased incidences and/or severities of bilateral retinal degeneration attributed to the greater lifetime exposure to light due to a higher survival rate in these groups.

The highest doses tested in carcinogenicity studies in mice and rats resulted in exposures (AUC0-24 h) that were equivalent (mice) and up to approximately 10 times greater than (rats) exposure at the maximum recommended dose in humans (30 mg). The highest non-tumorigenic exposure in female rats was approximately 7 times the human exposure at the recommended dose.

Additional clinical data after the granting of the MA for the oral formulation suggested that aripiprazole did not have any systematic biochemical effect upon the adrenocortical hormones. These data were considered reassuring and in line with the conclusion that the tumours observed in the female rats were species specific.

Reproduction Toxicity

The full standard battery of reproduction toxicity studies was conducted in rats and rabbits with aripiprazole.

The following findings point to hazard caused by aripiprazole administration during reproduction: (i) oral administration of aripiprazole to pregnant rats at doses of 20 and 30 mg/kg/day from days 7 to 17 of gestation produced evidence of maternal toxicity and suppressed fetal growth (decreased body weight and retarded ossification); (ii) in the study of embryo-fetal development in rats, fetal abnormalities (with low incidence) were observed at the dose of 30 mg/kg in almost all types of abnormalities evaluated. In some cases, abnormalities were also observed at 3mg/kg. Noteworthy, it was observed a dose-dependent decrease in fetal ossification, which became statistically significant at 30 mg/kg. Dose-related maternal toxicity and a slight delay in vaginal opening in F1 females occurred at 10 and 30 mg/kg/day. A maternal dose of 30 mg/kg/day resulted in slight prolongation of gestation,

developmental delay of F1 fetuses and pups, and minimally decreased reproductive performance (fertility index) of F1 rats; (iii) In a supplemental embryo-fetal development study in rats, decreased body weight on day 4 postpartum and a tendency for delayed vaginal opening and an increase in pre-implantation loss occurred at 30 mg/kg/day in F1 females; (iv) In the study of embryo-fetal development in rabbits, fetal body weights were decreased in males at 30 mg/kg/day and in both sexes at 100 mg/kg/day. Other drug-related changes at 100 mg/kg/day included: abortion in seven dams, minimal maternal body weight loss during the treatment period, increased post-implantation loss, decreased placental weight, and increased incidences of common skeletal variations (20 thoraco-lumbar vertebrae and extra 13th rib and fused sternebrae.

NOELs for embryo-fetal and peri/postnatal development occurred at subtherapeutic or low multiples of the human steady-state exposures to aripiprazole and its active metabolite, OPC-14857.

Toxicokinetic data

Toxicokinetic data were collected from the toxicology studies specifically conducted with aripiprazole IM depot.

Exposure to aripiprazole with IM injection was prolonged with the parent compound detected at 29 days or more following a single injection. With repeat dosing, systemic levels of aripiprazole and metabolites increased with dose and the increase was not generally dose proportional. There were no remarkable differences between genders. No new metabolites or decomposition products of aripiprazole were formed at the injection site. Exposure profiles of aripiprazole and metabolites vary across the different non clinical species (rats, dogs and monkeys) although the exposure to aripiprazole was higher than those for the metabolites. There was no dose proportionality across species. With extended treatment from 26 to 52 weeks in dogs, there were minimal differences in Cmax and AUC for aripiprazole or metabolites. The plasma levels, based on Cmax, of the metabolites OPC-14857 and DM-1452 tended to be greater in dogs compared to rats, and OPC-14857 plasma levels tended to be higher in dogs than in monkeys. In contrast, the plasma levels for DM-1451 was about 4-fold higher in rats compared to dogs. Other metabolites, eg, OPC-3373 and DCPP were generally similar between rats and dogs.

Local Tolerance

Seventeen IM injection local tolerance studies with aripiprazole were conducted in rats, rabbits, dogs and monkeys. Nine of the studies were exploratory and aimed to determine an appropriate vehicle for aripiprazole formulations that could be used in subsequent toxicity studies. Results indicated a better tolerance for formulations using CMC, HPC or 15% Captisol as vehicle.The remaining 8 pivotal local tolerance studies were conducted using formulation with CMC or 15% Captisol.

In rats, after a single dose of 12.5, 25 or 50 mg/kg (CMC formulation), a dose-related increased incidence of injection site swelling was observed and likely represented deposits of test article in the muscle. There was a greater incidence in males, compared to females. At the injection sites, white discolored foci were observed at necropsy on Days 29 and 45 at all doses although the size of the foci generally decreased over time but did not completely resolve by Day 45 (study termination). The foci were characterized microscopically by a dose-related minimal to mild granulomatous inflammation and minimal fibroplasia/fibrosis on Day 29. The localized inflammatory response consisted of numerous epithelioid macrophages and foreign body giant cells in association with deposits of birefringent crystals (interpreted as drug) in the muscle interstitium. These findings were considered a foreign body reaction to deposited drug. By Day 45, partial resolution of the granulomatous inflammation and fibroplasia/fibrosis had occurred. In another rat study using a different CMC formulation and doses (75

or 100 mg/kg as a single administration), there were no drug-related injection site findings. Microscopically, the primary finding at the injection site was a localized, minimal to mild granulomatous inflammatory response to deposited drug that was consistent with a foreign-body reaction. This inflammation was not completely resolved by Day 45. No evidence of skeletal muscle injury at the injection sites was observed at either dose. After repeated dose of 1 or 3.75 mg/kg/day once daily for 2 weeks using Captisol formulation, a dose-related increased incidence of discoloration and swelling at injection sites was observed during the dosing phase. These findings resolved by Day 17 after 3 days of recovery. At the end of the dosing phase, a statistically significant increase in the mean serum AST was observed in females at the high dose. No effects on either AST or CPK levels were observed in either gender at the end of the recovery phase. At necropsy, a minimally increased incidence of dark and/or red discoloration of injection sites was present. Microscopically at the injection sites, degeneration, necrosis, and regeneration of muscle and sub-acute inflammation, hemorrhage, edema, and fibroplasia/fibrosis of muscle and surrounding connective tissue occurred at a generally minimal severity in the vehicle and 1 mg/kg/day groups and at a minimal to mild severity in the 3.75 mg/kg/day group. In all dose groups, the fibroplasia was located primarily in connective tissue adjacent to the muscle, with lesser involvement of IM connective tissue in most animals. During the 2-week post-dose period, there was nearly complete reversibility of injection site changes. Only minimal, late stage muscle regeneration and fibroplasia/fibrosis were still present in vehicle control, 1 and 3.75 mg/kg/day animals.

In rabbits, after single doses of 25,50 or 100 mg (CMC formulation) and at necropsy, white discoloration at the injection sites (consistent with deposits of the test article and associated inflammation) was noted in all drug-treated animals at all timepoints. The size of these discolored foci was generally dose related, and there was a reduction in size over time. The principal microscopic finding at the injection site was generally dose-related and was observed as minimal to moderate granulomatous inflammation in the muscle interstitium. The localized granulomatous inflammation was characterized by the presence of numerous epithelioid macrophages and lesser numbers of heterophils and lymphocytes and was most severe at Days 15 and 29, with incomplete resolution by Day 57. The finding was considered to represent a foreign body reaction to deposited drug. Additional drug-related microscopic findings included minimal to mild sub-acute inflammation through Day 15 in the 25 and 50 mg dose groups and through Day 57 in the 100 mg dose group, an increased incidence of minimal muscle degeneration/regeneration, and minimal or mild fibroplasia that generally resolved by Day 57. Birefringent polymorphic crystalline material, interpreted as deposited drug, remained in areas of inflammation through Day 57 for all treated groups. In another rabbit study using single doses of 100 or 200 mg (CMC formulation), mild edema at the injection site was noted in 1 rabbit on Day 2 and persisted to Day 4 (day of necropsy). At necropsy, white and/or red discoloration at the injection site were seen in all treated animals at scheduled sacrifices on Days 4, 7, 15 and 29. At the Day 57 necropsy, tan discoloration was noted at the injection site in the treated rabbits at both doses. These foci of white/tan discoloration at the injection sites were considered to be deposited test article, and the deposits were generally comparable in size through Day 29 but were notably smaller on Day 57. Microscopic finding at the injection site at all timepoints included minimal to moderate (generally mild) granulomatous inflammation as a foreign-body reaction in response to deposited drug (polymorphic, birefringent crystalline material). The inflammatory reaction was most severe on Day 15 but declined in severity through Day 57. Other drug-related findings indicative of skeletal muscle injury included minimal degeneration and necrosis (Days 4 and/or 7) and minimal regeneration (Day 15). Additionally, mild sub-acute inflammation was observed at the injection sites through Day 15. After single dose of 2, 4 or 7.5 mg using Captisol formulation, very slight to slight injection site edema was observed across all groups including controls. Increased CPK level was observed for all groups, including controls, relative to pre-dose values. A dose-related increased CPK level on Day 2 was observed compared to (saline) controls but were similar across all groups at Day 18. At the Day 4

necropsy, focal tan areas associated with and/or surrounded by hemorrhage were observed at injection sites of some animals receiving 4 and 7.5 mg/mL. Microscopically, muscle degeneration/regeneration and inflammation were observed on Day 4 with minimal severity in the saline control group and minimal to mild severity in the vehicle control, 2, and 4 mg/mL groups and mild to moderate severity in the 7.5 mg/mL group. Additionally, minimal to mild hemorrhage and mineralization of degenerate muscle fibers were noted in vehicle- and drug-treated groups. By Day 18, minimal muscle regeneration and mineralization were still present in one animal at 2 mg/mL, and very slight edema and minimal muscle regeneration, inflammation, mineralization, and/or perimysial/endomysial fibrosis were apparent at 7.5 mg/mL.

In dogs, single doses of 200,300 or 400 mg (CMC formulation) were administered as 2 injections. At 300 and 400 mg doses, swelling and erythema were evident at the injection sites. At necropsy, white discoloration (deposits of the test article) was apparent at the injection sites of all dogs, and red discoloration of subcutaneous tissue (hemorrhage) and minimal or mild swelling were noted in dogs in the 300 and 400 mg dose groups. Microscopically, the primary tissue response to deposited drug (birefringent crystalline material) was mild sub-acute inflammation at the 200 mg dose with moderate to marked sub-acute inflammation in dogs given the higher doses. Other microscopic injection site changes observed in one or both dogs given each dose volume were minimal to mild in severity and included: edema, hemorrhage, degeneration of skeletal muscle, granulomatous inflammation, and fibroplasia/fibrosis.

In monkeys, after single doses of 50 or 100 mg, hypoactivity (1 female), acute injection site swelling or discoloration (female/male) were noted at highest dose tested. There was a drug related increase in AST (1.4-fold to 6.3-fold) and CPK levels (3-fold to 18.7-fold) in both sexes on Day 2 post-dose, after 50 mg (CMC) and 100 mg (saline) dose. On Days 4 and 7 post-dose, minimal changes in AST and CPK levels were observed. At necropsy, white discoloration, apparent test article deposits in muscle, was noted in the injection sites through Day 29 for both concentrations. The white foci were of variable shape and size and did not decrease with time. Microscopically, the principal finding was a minimal to mild granulomatous inflammatory response to birefringent crystalline drug deposits that was characterized by accumulation of macrophages with foamy cytoplasm and eosinophilic deposits of the test article. The severity of the microscopic changes tended to decrease with time, but complete resolution of the inflammatory process did not occur by Day 29. Minimal focal inflammation and skeletal muscle regeneration was observed in the injections sites from CMC and saline administration as a consequence of needle damage from injection.

Other toxicity studies

No other toxicity studies were specifically performed with aripiprazole IM depot.. Available studies derived from oral aripiprazole.

Antigenicity: Aripiprazole was evaluated for its antigenic potential in groups of 10 male Hartley guinea pigs sensitized with doses of 0.5 or 5 mg/kg of aripiprazole in Freund's complete adjuvant (FCA). No antigenic potential in guinea pigs was found.

Immunotoxicity:
In rats, no significant change in the T-cell dependent antibody response to sheep red blood cell antigen occurred at oral doses up to 60 mg/kg/day in a 4 week study, indicating the humoral response was unaltered by treatment with aripiprazole. No clear drug-related morphologic changes in lymphoid and hematopoietic tissues of rodents and monkeys were observed in repeat-dose toxicity studies of aripiprazole. Minimal bone marrow depletion was observed in rats at 20 mg/kg/day in the 5-week screening study and at 60 and 100 mg/kg/day in the 4-week toxicity study.

Dependence: The physical dependence and abuse potential of aripiprazole were evaluated in three pivotal studies: a primary physical dependence study in rats, a primary physical dependence study in

monkeys, and a self-administration substitution test in monkeys. The obtained results suggest that aripiprazole does not have significant abuse liability.

Metabolites:
A single-dose intravenous toxicity study of OPC-14857 in rats showed at 50 and 100 mg/kg, clinical signs of poor general condition partially reversible on day 2, with evidence of intravascular haemolysis. In the single-dose intravenous toxicity study of OPC-3373 in rats, there were no drug-related effects. A bacterial reverse-mutation test of DCPP was negative.

Photo-safety:
As aripiprazole binds to melanin-containing tissues (tissue distribution studies), in vitro (photostability, 3T3 NRU PT) and in silico studies were performed and did not indicate a risk to patients.

2.3.5. Ecotoxicity / environmental risk assessment

Table 1. Summary of environmental fate / effects for aripiprazole

Substance (INN / Invented Name): Abilify Maintena					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	FDA guideline 3.02	log K_{ow} pH 5 = 2.70 log K_{ow} pH 7 = 2.95 log K_{ow} pH 9 = 2.86			Potential PBT (**N**)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	≤ 4.5			**not B**
	BCF	----------			----------
Persistence	DT50 or ready biodegradability	177 days (water/sediment), 210 days (soil) at 20°C			**P**
Toxicity	NOEC	2.61 µg/L			**T***
PBT-statement :	**The compound is not considered as PBT nor vPvB**				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} ≥ 10 000 High affinity for 4 test soils and activated sludge			K_{oc} from 10 900 to 106 000 L / Kg
Ready Biodegradability Test	OECD 301	----------			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 0.43 and 6.47 days $DT_{50, whole\ system}$ = 177 and 30.9 days % shifting to sediment = 68.7 and 37.7 % at day 14			Two aquatic sediments
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition	OECD 201	NOEC	140.0	µg/L	*Pseudokirchneriella subcapitata*

Test/*Species*					
Daphnia sp. Reproduction Test	OECD 211	NOEC	2.61	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC (survival)	5.80	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	≥ 1000	mg/ L	Highest dose
Phase IIb Studies					
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	210 days 2.3%		for all 4 soils ≤3% metabolites
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	------	mg/ kg	No inhibition of nitrification organisms at 2000 mg / kg
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	100	mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	1000	mg/ kg	
Sediment dwelling organism Soil dwelling organism Collembola, Reproduction Test	OCDE 218 ISO 11267	NOEC NOEC (mortality)	≥100 0.150	mg/ kg mg/ kg	*Chironomids* *Folsomia candida*

* CHMP amended the conclusions for the toxicity of the active substance (aripiprazole) according to toxicity criteria and available data

2.3.6. Discussion on non-clinical aspects

No pharmacological studies were specifically conducted with IM aripiprazole depot in animals taking into account existing pharmacological data for oral aripiprazole and its metabolites and this was considered acceptable by the CHMP. The pharmacological properties of aripiprazole are mediated through a combination of partial agonism at dopamine D2 and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2A receptors.

The pharmacokinetic profile of aripiprazole has also already been characterised with oral and IM rapid aripiprazole (crosses the blood brain barrier, placenta transfer, >99% plasma protein binding; excretion into faeces; urine and notably milk). Aripiprazole was completely bioavailable following IM and SC administration. No new metabolites were formed following IM administration. Aripiprazole injected as a depot formulation remained at the injection site without being metabolised or decomposed for a long time and was eliminated by approximately 168 hours. At similar doses, higher exposure (determined by Cmax and AUC) were observed using the oral route as compared to the IM depot injection indicating that extrapolation of the non clinical data from oral aripiprazole could be made. With oral aripiprazole, repeat-dose toxicity in rat and monkeys revealed mainly CNS-related effects. The NOAEL were mostly below the resulting human exposure at therapeutic dose (30 mg/day). The genotoxicity battery was positive in some tests, but at very high and cytotoxic concentrations. Overall, based on the weight of evidence from the whole battery of genotoxicity studies, aripiprazole was not considered to pose a genotoxic risk to humans at therapeutic doses and exposures. The main finding in carcinogenicity was an increased incidence of adrenocortical tumors in rats. Additional clinical data suggested that aripiprazole did not have any systematic effect upon adrenocortical hormones, indicating that the observed tumours in female rats were probably species specific. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were

observed in rats at doses resulting in subtherapeutic exposures (based on AUC) and in rabbits at higher exposure.

The toxicology studies conducted with the aripiprazole IM depot showed a toxicological profile generally similar to oral aripiprazole to the exception of local tissue responses to injection of the depot observed in the extensive data package investigating local tolerance. The severity of the tissue reactions was proportional to the dose volume, the drug concentration at the injection site and the frequency of injections, and the changes were fully or partially reversible following cessation of administration. Gross and microscopic evidence of injection site inflammation at all doses with incomplete recovery were noted in every studies across different animal species. These were in fact the principal drug-related findings in the toxicity studies in rats, dogs and monkeys specifically conducted with the IM depot. According to the applicant, the vehicle (Captisol) may have contributed to some extent to the local tissue responses and trauma associated with the injection, with a slight exacerbation of the injection site injury related to aripiprazole. Whilst local site injection reactions are further discussed from a clinical perspective (see 2.6), a description of these findings (granulomatous inflammation, foci, cellular infiltrate, swelling, fibrosis) in section 5.3 was considered adequate by the CHMP.

Based on estimated sale forecast for 2015 for aripiprazole, no additional impact to the environment was expected with the use of IM aripiprazole depot.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non clinical aspects of aripiprazole IM depot have been adequately documented and meet the requirements to support this application.

2.4. Clinical aspects

2.4.1. Introduction

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.

A routine GCP inspection was performed at one investigator site for study 31-07-247 and two investigator sites for study 31-07-246. Overall, three major findings and a number of minor findings were reported by the inspectors. No critical findings were reported at any site. The GCP inspectors concluded that the sites inspected appeared to be GCP compliant and therefore recommend the acceptance of the data. The CHMP considered that the GCP findings reported did not impact on the study results and conclusions.

2.4.2. Pharmacokinetics

The Phase I clinical pharmacology program (studies CN138-020, 31-07-002 and 31-05-244, 31-11-289) has been conducted in patients with schizophrenia and schizoaffective disorder.

In addition to these phase I studies specifically conducted with IM aripiprazole depot, a population pharmacokinetic analysis was performed using data from Phase I and III studies (CN138020, 31-07-246) together with Phase I studies from the clinical development of oral aripiprazole (studies 31-98-206,31-98-207). An external validation of the population PK model was obtained from this analysis

using the Phase III study 31-07-247 and was considered adequate by the CHMP. Finally, pharmacokinetic characteristics derived from studies with oral (mainly) and IM rapid aripiprazole, were also considered.

Plasma concentration of aripiprazole and analysed metabolites (e.g dehydro-aripiprazole) was determined using high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS) method in the pharmacokinetic (PK) studies. Pharmacokinetic parameters were determined using non compartmental models. Population PK analyses were conducted using non linear mixed effects modeling methodology (NONMEM).

Absorption

Following a single IM dose of aripiprazole depot ranging from 15 to 400 mg, the plasma concentrations of aripiprazole gradually increase to reach maximum plasma concentrations within 7-24 days (167-577 hours). The release of the drug starts as early as day 1 and the estimated time required to absorb 50% of the dose ranged between 10 to 35 days across the tested dose range. The average absorption half life of IM aripiprazole depot was 28 days. After IM multiple dosing, the plasma concentrations of aripiprazole gradually rise and at steady state reach maximum plasma concentrations at a median Tmax of 5-7 days. Dehydro-aripiprazole, the active metabolite, represents about 29.1-32.5 % of aripiprazole AUC in plasma.The absorption of aripiprazole from the IM depot formulation was considered complete relative to the IM standard (immediate-release) formulation. Relative bioavailability of the IM aripiprazole depot compared with the IM rapid aripiprazole (5 mg) indicated a supra-bioavailability (based on AUC) ranging from 1.10 to 1.44 for all doses, except for the lower dose of 15 mg. The dose adjusted Cmax values for the IM aripiprazole depot were approximately 5% of the Cmax from the IM rapid aripiprazole. A direct comparison with IV aripiprazole has not been performed and was not considered necessary.

Comparison of exposure with oral aripiprazole

Simulation of median aripiprazole concentration and its estimated fifth and 95th percentiles after administration of 400 mg IM aripiprazole depot at dose initiation and at steady-state and comparison to that of 10 and 30 mg oral aripiprazole are presented in Figure 1. Based on simulations using the population pharmacokinetic analysis, the median aripiprazole concentrations after an initial IM depot administration (solid black line, left panel) and its estimated lower fifth percentiles aripiprazole concentrations (hashed black line, left panel) were similar to that of the concentrations achieved by administration of 10 mg oral aripiprazole. At steady state, the median aripiprazole concentration (solid black line, right panel) and its estimated lower fifth and upper 95th percentiles aripiprazole concentrations (hashed black lines, right panel) were within the concentrations achieved by administration of 10 to 30 mg daily oral aripiprazole.

Additional simulation of aripiprazole median and its fifth and 95th percentiles up to 16 aripiprazole administrations and comparison with that of 10 and 30 mg aripiprazole administered as an oral tablet are presented in Figure 2.

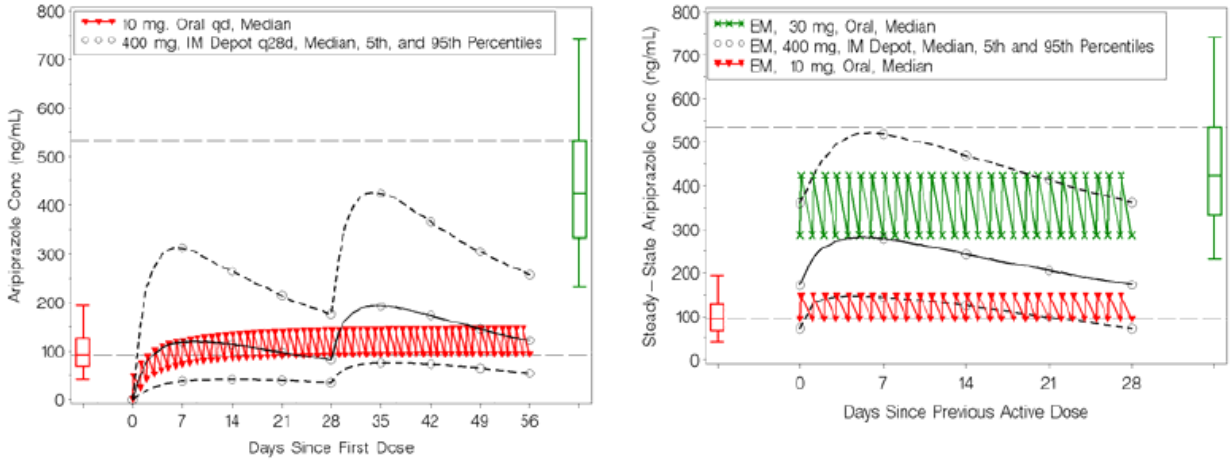


Figure 1 Simulation of Aripiprazole Median (Solid Line) and 5th and 95th Percentiles (Hashed Line) After Administration of 400 mg Aripiprazole IM Depot at Dose Initiation (Left Panel) and at Steady-State (Right Panel) and Comparison to 10 mg Oral, and 30 mg Oral

Red box and whiskers: 5th to 95th percentiles for Cmin for 10 mg daily oral aripiprazole.
Green box and whiskers: 5th to 95th percentiles for Cmax for 30 mg daily oral aripiprazole.
Horizontal dashed lines represent the therapeutic range associated with 10-30 mg administration of daily oral aripiprazole.
Source: Post-hoc analysis based on population PK model CSR 31-11-287 (programming source:202420/d1pk-300vs400quest-ema/l-startup-cpvsday.sas, l-allem-cpvsday-oralover-p595.sas).

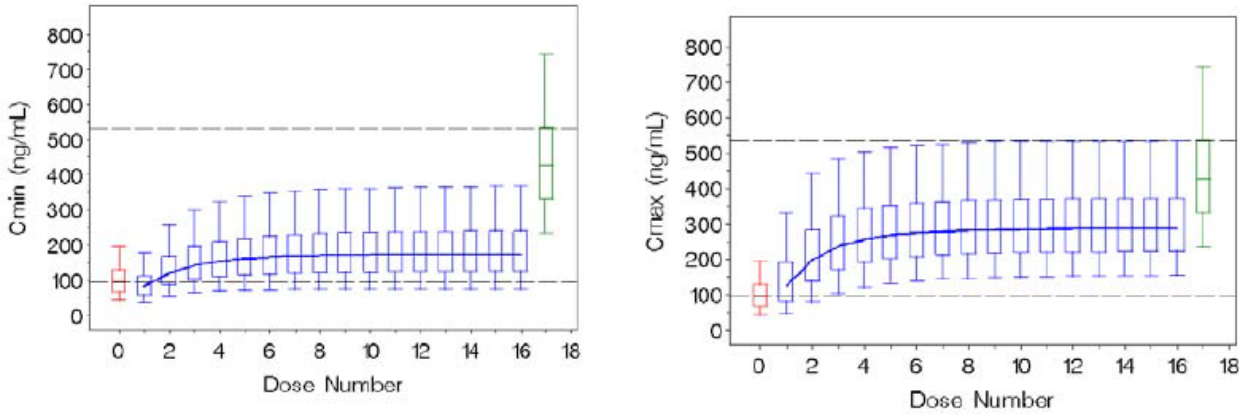


Figure 2 Simulation of Aripiprazole PK Parameters after Administration of 400 mg Aripiprazole IM Depot and Comparison to 10 mg Oral, and 30 mg Oral Dosing

Red box and whiskers: 5th to 95th percentiles for Cmin for 10 mg daily oral aripiprazole.
Green box and whiskers: 5th to 95th percentiles for Cmax for 30 mg daily oral aripiprazole.
Horizontal dashed lines represent the therapeutic range associated with 10-30 mg administration of daily oral aripiprazole.

Source: Figure A10.6-1 CSR 31-11-287.

Distribution

No specific distribution study has been performed with the IM aripiprazole depot and this was considered acceptable taking into account that the distribution profile of aripiprazole has already been characterised with the studies previously conducted for the oral aripiprazole MA.

Aripiprazole is highly bound to plasma proteins (99%). However its steady-state volume of distribution following i.v. administration is 404L or 4.94L/kg, indicating a higher affinity to tissue proteins. Dose dependent D2 receptor occupancy confirms that aripiprazole crosses the blood-brain barrier, as already

established from rat studies. No preferential distribution of aripiprazole to blood cells was established based on total blood to plasma activity ratio (approximately one) obtained after a 14C labelled 20 mg single dose of aripiprazole.

Following oral administration, aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 l/kg, indicating extensive extravascular distribution.

Elimination

Following multiple dose administration, the mean aripiprazole apparent terminal elimination half-lives for aripiprazole IM depot 300 mg and 400 mg doses differed significantly (29.9 days and 46.5 days, respectively and presumably due to absorption rate-limited kinetics.Following a single oral dose administration of [14C]-aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the feces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the feces.

Dose proportionality and time dependencies

Dose proportionality

Less than Dose-proportional increases in aripiprazole and de-hydro-aripiprazole exposures were observed after the 300 mg and 400 mg multiple doses of aripiprazole IM depot. It was noted that after single dose administration ranging from 15 to 400 mg, a lower exposure was observed at 400 mg as compared to 300 mg. This finding may be associated to the different volumes injected with the doses and/or different sites of administration used in the concerned studies and was considered of limited clinical relevance taking into account the data collected from phase III studies using the 400 mg as a starting dose (see 2.4).

Time dependency

No differences in PK steady state profiles were observed after repeated administrations (for 6 months in 31-05-244 and 44 weeks in 31-07-246), hence no significant time dependency for the pharmacokinetics of aripiprazole IM depot is expected.

Inter and Intra-individual variability

After multiple dose of IM aripiprazole depot, a higher variability in aripiprazole exposure was noted for the 400 mg dose. In the PK population analysis, the inter individual variability of 400 mg dose of IM aripiprazole depot was found in the range of 39-42% and thus not greater than oral aripiprazole tablets estimated in the range of 51-57%.

Special populations

Population pharmacokinetic analysis evaluating demographic variables (e.g race, gender, age) was conducted. The effect of BMI was also investigated. No studies in paediatric population with schizophrenia was performed in accordance with the waiver granted for all subsets of this population. Available information with oral aripiprazole was also considered.

With oral aripiprazole, no clinically relevant effect on race, gender, age, smoking, renal or hepatic function was observed.

After oral administration of aripiprazole, there are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects. Similarly, there was no detectable effect of age in a population pharmacokinetic analysis of IM aripiprazole depot in schizophrenia patients.

In a single-dose study with oral administration of aripiprazole, the pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to that in young healthy subjects.

A single-dose study with oral administration of aripiprazole to subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

Pharmacokinetic interaction studies

No pharmacokinetic interaction studies were performed with IM aripiprazole depot. Available information was derived from studies with oral aripiprazole. In addition, simulations and modelling based on these data and the population pharmacokinetic analysis used to characterise IM aripiprazole depot were performed to analyse whether dose adjustments should be considered in the following cases: CYP2D6 poor metabolisers, concomitant administration of CYP2D6 or CYP3A4 inhibitors.

In a clinical study with healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while Cmax was not changed. The AUC and Cmax of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects.

In a clinical study with healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and Cmax by 63% and 37% respectively. The AUC and Cmax of dehydro-aripiprazole increased by 77% and 43% respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. Other potent inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors, may be expected to have similar effects.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of Cmax and AUC were 68% and 73% lower, respectively, compared to when aripiprazole (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of Cmax and AUC after carbamazepine co-administration were 69% and 71% lower, respectively, than those following aripiprazole alone treatment.

When either valproate or lithium were coadministered with aripiprazole, there was no clinically significant change in aripiprazole concentrations.

Effects of on the pharmacokinetics of drugs, which are substrate for the isozymes involved in aripiprazole biotransformation, such as dextromethorphan (CYP3A4 and CYP2D6), warfarin (CYP2C9) and omeprazole (CYP2C19) were not significant.

Based on the simulation modelling data, CYP2D6 poor metaboliser subjects exhibited aripiprazole concentrations that were about twice that of CYP2D6 extensive metaboliser subjects. Long-term chronic administration of aripiprazole IM depot with either a CYP2D6 or a CYP3A4 inhibitor with the 300 mg IM depot (for subject receiving 400 mg aripiprazole IM depot) and 200 mg IM depot (for subject receiving 300 mg aripiprazole IM depot) resulted in steady-state median aripiprazole concentrations within the therapeutic window during the entire dosing interval. Long-term chronic administration of

aripiprazole IM depot with both a CYP2D6 and a CYP3A4 inhibitor with the 200 mg IM depot (for subject receiving 400 mg aripiprazole IM depot) and 160 mg IM depot (for subject receiving 300 mg aripiprazole IM depot) resulted in steady-state median aripiprazole concentrations within the therapeutic window. Long-term chronic administration of 200 mg aripiprazole IM depot with a CYP3A4 inhibitor in subjects who are known poor metabolizers of CYP2D6 resulted in steady-state median aripiprazole concentrations comparable with that of 300 mg aripiprazole IM depot and within the therapeutic window during the entire dosing interval.

2.4.3. Pharmacodynamics

Mechanism of action

Aripiprazole mechanism of action is suggested to be mediated through a combination of partial agonist at dopamine D2 receptors and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2 receptors.

Primary and Secondary pharmacology

Primary and secondary pharmacology have already been characterised with studies with oral aripiprazole which consisted in a single pharmacodynamic study (Study 31-94-201) and a pharmacodynamic interaction study between aripiprazole and alcohol (Study 31-00-230).No specific study with IM aripiprazole was conducted.

Study 31-94-201 was conducted to determine the degree of brain D2 receptor occupancy induced by aripiprazole by PET scanning. A dose-dependent increase in dopamine D2 receptor occupancy was observed at doses ranging from 0.5mg/day to 10 mg/day. Receptor occupancy approached saturation at 10 mg/day with approximately 85% receptor occupancy; at 30 mg/day, the next dose level evaluated, receptor occupancy was approximately 80%-95%. Receptor occupancy at the 0.5-mg/day dose level was approximately 23% - 46%. No data on the binding to other relevant receptors, namely 5-HT2, are provided.

Study 31-00-230 was conducted to assess the potential for pharmacodynamic interactions between orally co-administered aripiprazole and ethanol. There were no differences in the gross motor skills or cognitive abilities when ethanol was added to aripiprazole and placebo. However due to variations in placebo effect it was not possible to determine if co-administration of aripiprazole with ethanol had a meaningful impact on cognitive function. Therefore, as mentioned in the SmPC, concomitant intake of alcohol with aripiprazole is not recommended.

2.4.4. Discussion on clinical pharmacology

The absorption and elimination profile of IM aripiprazole depot has been adequately characterised. Available information on the distribution, metabolism derived mainly from studies with oral aripiprazole and this was considered acceptable by the CHMP.

Following a single IM dose of aripiprazole depot ranging from 15 to 400 mg, the plasma concentrations of aripiprazole gradually increase to reach maximum plasma concentrations within 7-24 days (167-577 hours). The release of the drug starts as early as day 1 and the estimated time required to absorb 50% of the dose ranged between 10 to 35 days across the tested dose range. The average absorption half life of IM aripiprazole depot was 28 days. The absorption of aripiprazole from the IM depot formulation was considered complete relative to the IM standard (immediate-release) formulation. Additional simulations using the population pharmacokinetic analysis confirmed that similar exposure

was achieved for IM aripiprazole depot (400 mg dose) and oral aripiprazole (10-30 mg) within an acceptable time window. No specific studies investigating special populations and drug-drug interactions were performed. Information related to renal, hepatic impairment, elderly derived from oral aripiprazole and are reflected in the SmPC accordingly.

Population pharmacokinetic analysis did not suggest effects of race, gender, age, BMI. Based on the knowledge on oral aripiprazole interactions with CYP2D6 inhibitors and CYP3A4 inhibitors/inducers, additional simulations were performed and specific dosing reduction were introduced in the SmPC in case of concomitant treatment greater than 14 days and in case of CYP2D6 known poor metabolisers. An additional precautionary SmPC statement was introduced for the dosing recommendation on CYP2D6 or CYP3A4 inhibitors pending further modelling from the applicant, as recommended by the CHMP. In the absence of data on concomitant use of CYP3A4 inducers, the SmPC information also recommends to avoid such association for more than 14 days.

During the evaluation (see 2.5.3), the applicant followed the CHMP recommendation to change the indication to the following: "maintenance treatment of schizophrenia in adult patients stabilized with oral aripiprazole". Consequently and on the basis of the clinical data available in patients orally stabilized with oral aripiprazole, no further data were considered by the CHMP necessary to address switching situations.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacological profile of aripiprazole IM depot in human studies has been adequately characterised.

2.5. Clinical efficacy

The initial indication applied for is: maintenance treatment of schizophrenia in adults.

The clinical development included long term studies investigating the maintenance of the effect. Maintenance was studied in one placebo controlled withdrawal study and one active controlled non inferiority study (versus oral aripiprazole).

In both studies, the injection site was the gluteal muscle and the needle length for the injection was selected based on BMI (21 gauge, 1.5 inch for BMI ≤ 28 kg/m2; 21 gauge, 2 inch for BMI > 28 kg/m2).

A tabulated summary of the efficacy studies are presented in Table 2.

Table 2. Efficacy studies

Study	Objective	Design	Dosing	Duration
31- 07–246	Maintenance of effect, Superiority versus placebo	DB, randomized withdrawal, placebo-controlled, flexible doses with prior conversion and stabilization with oral aripiprazole 10-30 mg/day	400 mg or 300 mg once monthly with oral aripiprazole 10-20 mg/day for the first 2 weeks	Conversion to oral aripiprazole: 4-6 weeks Oral stabilization: 4-12 weeks IM depot stabilization:12-36 weeks Maintenance: up to 52 weeks

31-07-247	Maintenance of effect, non inferiority versus oral aripiprazole daily	DB, active controlled, flexible dose regimens of aripiprazole IM depot with prior conversion and stabilization with oral aripiprazole10-30 mg per day (10 or 15 mg tablets) oral aripiprazole 10-30 mg/day	400 or 300 mg once monthly; 50 or 25 mg once monthly with oral aripiprazole 10-20 mg/day for the first 2 weeks	Conversion to oral aripiprazole: 4-6 weeks Oral stabilization: 8-28 weeks Maintenance: 38 weeks

DB: double blind

Taking into account the design of study 31-07-246 that did not include a direct comparison with oral aripiprazole and used a different primary efficacy endpoint than study 31-07-247, the CHMP considered the active controlled study 31-07-247 as the pivotal study.Study 31-07-246 is regarded as supportive of the present application.

An additional non inferiority study versus oral aripiprazole (6-24 mg/day) using doses of 400 mg or 300 mg is ongoing with a different dosing regimen for oral supplementation (6-12 mg/day) during the first 2 weeks.Long term open label studies are also ongoing (studies 31-08-248, 31-10-270, 31-11-283 and 31-11-284) mainly investigating the long term safety of IM aripiprazole depot.. Interim data (cut off date: April 2012) related to these studies are presented as supportive of safety profile of the IM aripiprazole depot (see 2.6).

2.5.1. Dose response study

No specific dose-response study was conducted for IM aripiprazole depot.. The choice of the doses for the phase III studies (400 mg and 300 mg) was based on PK data from multiple dose study 31-05-244 and single dose study CN138-020 and efficacy/safety data of oral aripiprazole 10-30 mg.

Studies 31-05-244 and CN138-020 suggested efficacy of IM aripiprazole depot at 400 mg and 300 mg doses, while once-monthly administration of the 200 mg IM depot injections did not result in mean aripiprazole through plasma concentrations that were comparable to the therapeutic concentrations of 10 mg to 30 mg oral aripiprazole administered daily to subjects with schizophrenia.

Study 31-05-244 included 3 doses (200, 300 and 400 mg) administered once every 28 days for a total of 5 monthly doses. This study suggested that the initial administration of 400 mg IM depot resulted in mean aripiprazole trough plasma concentrations, prior to the administration of the second IM depot administration, that were equal to or greater than steady-state aripiprazole concentrations corresponding to 10 mg oral aripiprazole (lowest effective oral dose in patients with schizophrenia). Consequently, the 400 mg dose was selected for further evaluation in the phase III trials as initiation dose and 300 mg dose used in the flexible dose regimen.

At the CHMP request, additional simulations of dose initiation with 300 mg aripiprazole IM depot in subjects stabilized on 10-15 mg oral aripiprazole with and without 10 mg oral aripiprazole

administration for 14 days were provided to support the exclusion of the 300 mg dose as initiation dose as well as simulation of dose initiation with 300 mg, followed by 300 mg aripiprazole IM depot in subjects stabilized on 10-30 mg oral aripiprazole with and without oral aripiprazole administrations for 14 days. These data predicted median aripiprazole trough concentrations lower than that of the pre-dose concentrations (prior to administration of 300 mg aripiprazole IM depot) and were considered as sufficient evidence by the CHMP to exclude the 300 mg as starting dose.

2.5.2. Main study

This was a double-blind, randomised, active-controlled, parallel-group study **(31-07-247)** evaluating the efficacy and safety of flexible dose monthly regimens of IM aripiprazole depot (400 or 300 mg; 50 or 25 mg) with prior conversion and stabilization with oral aripiprazole versus oral aripiprazole 10-30 mg/day followed up by 38 weeks of treatment (see Figure 3- screening and treatment).

Figure 3

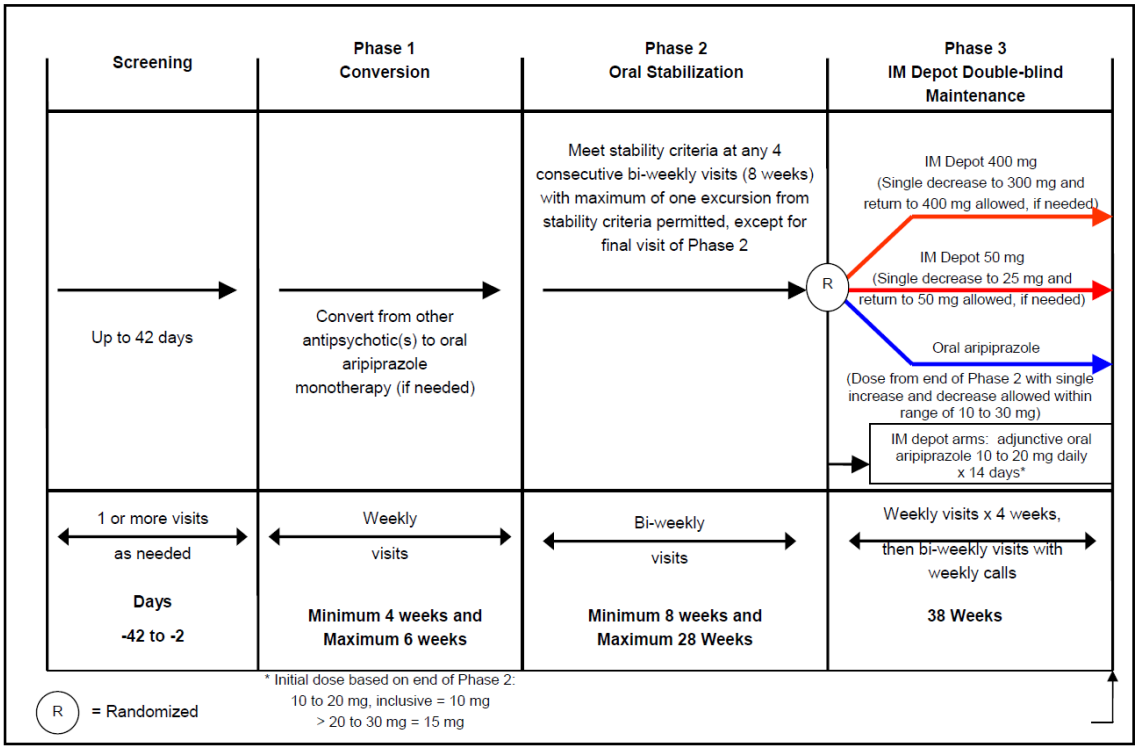


Figure 5.1-1 Trial Design Schematic - Screening and Treatment

The study was conducted in the following countries: Austria, Belgium, Bulgaria, Chile, Croatia, Estonia, France, Hungary, Italy, South Korea, Poland, South Africa, Thailand, and United States (US).

2.5.2.1. Methods

Study Participants

Main inclusion criteria

Male and female subjects, aged 18 to 60 years: with a current diagnosis of schizophrenia as defined by DSM-IV-TR criteria and a history of the illness for at least 3 years prior to screening; who had a history of symptom exacerbation with interruption or discontinuation of antipsychotic treatment, who were currently being treated with one or more antipsychotic(s) other than clozapine and who, in the

investigator's judgment, required chronic treatment with an antipsychotic medication and would benefit from treatment with an aripiprazole IM depot formulation.

Prior to receiving aripiprazole IM depot treatment, subject enrolled were converted (up to 6 weeks) and stabilised with oral aripiprazole for a minimum of 8 consecutive weeks.

Main exclusion criteria

Exclusion criteria mainly included: subjects with a current DSM-IV-TR diagnosis other than schizophrenia (e.g schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, amnestic or other cognitive disorders); subjects with borderline , paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder; with significant risk of violent behaviour or a significant risk of committing suicide based on history or investigator's judgment, subjects treated with CYP3A4 inhibitors/inducers and CYP2D6 inhibitors (at all phases); antidepressants, other antipsychotics, mood stabilisers after screening phase; electroconvulsive therapy (within 180 days prior to entry into the stabilisation phase); subjects who had more than one excursion from stability (as per criteria) after achieving a response to oral aripiprazole at a point in the trial where they would not be able to maintain oral stabilisation; subjects who had not achieved stability by 28 weeks of oral stabilisation or who had consecutive excursions at weeks 20 and 22.

Treatments

Subjects eligible for the double-blind, active-controlled phase were randomly assigned in a 2:2:1 ratio to double-blind treatment to one of 3 treatment groups, stratified by region (US and non-US): 1) aripiprazole IM depot 400 mg/300 mg, 2) the stabilization dose of oral aripiprazole 10-30 mg, or 3) aripiprazole IM depot 50 mg/25 mg. The aripiprazole IM depot 50 mg/25 mg dose was included as a low-dose aripiprazole group to test assay sensitivity for the non-inferiority design. Each subject randomized to oral aripiprazole was randomly assigned to a placebo group to match the administration procedure for either the aripiprazole IM depot 400 mg/300 mg group or the aripiprazole IM depot 50 mg/25 mg group. In addition, concomitant double-blind oral aripiprazole was given for 2 weeks to maintain therapeutic plasma concentrations.

Eligible subjects who either completed or were withdrawn for any reason after at least one dose of study medication in the double-blind, active-controlled Phase of Trial 31-07-247 had the option to enter a 52-week, long-term, open-label safety trial (Trial 31-08-248).

Patients randomized to oral aripiprazole received the same aripiprazole dose that they were stabilized on during the stabilization phase.

Objectives

The primary objective was to compare two dosing regimens of IM aripiprazole depot (400 or 300 mg; 50 or 25 mg) versus oral aripiprazole (10-30 mg/day) in patients with schizophrenia, converted and stabilised with oral aripiprazole.

The secondary objective was to evaluate the safety and tolerability of the two dosing regimens of IM aripiprazole depot versus oral aripiprazole (10-30 mg/day), followed up by 38 weeks of treatment, in patients with schizophrenia, converted and stabilised with oral aripiprazole.

Outcomes/endpoints

The primary endpoint was the estimated proportion of subjects experiencing impending relapse by end of 26 weeks from the date of randomization in the maintenance phase, in subjects with schizophrenia

stabilised with oral aripiprazole a minimum of 8 consecutive weeks. Secondary endpoints included time to impending relapse from the date of randomization in the maintenance phase, percentage of responders (defined as stabilised patients at Week 38), Percentage of subjects achieving remission (defined as a score of≤ 3 on each of the following specific PANSS items, maintained for a period of 6 months: delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6), mean changes from baseline to endpoint in PANSS total score, CGI-S, PANSS positive and negative subscales and personal and social performance (PSP) score, mean CGI-I score at endpoint, time to discontinuation due to all causes.

Impending relapse was defined as meeting any or all of the following 4 criteria: 1) Clinical Global Impression of Improvement (CGI-I) of ≥ 5 (minimally worse) and either an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score > 4 with an absolute increase of ≥2 on that specific item since randomization or an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score > 4 and an absolute increase of ≥4 on the combined 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization; 2) Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), but excluding hospitalization for psychosocial reasons; 3) Clinical Global Impression of Severity of Suicide (CGI-SS) of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2 and 4) Violent behavior resulting in clinically relevant self-injury, injury to another person, or property damage.

Stabilised patients were defined as fulfilling all of the following criteria for 8 consecutive weeks :1) outpatient status , 2) PANSS total score ≤80, 3) Lack of specific psychotic symptoms on the PANSS as measured by a score of ≤4 on each of the following items (possible scores of 1 to 7 for each item: conceptual disorganization, suspiciousness, hallucinatory behaviour, unusual thought content), 4) CGI-S ≤4 (moderately ill), 5) CGI-SS ≤2 (mildly suicidal) on Part 1 and ≤5 (minimally worsened) on Part 2.

Sample size

The sample sizes were estimated to achieve about 93% power for the primary non-inferiority comparison at an alpha level of 0.05 (two-sided) using large sample normal approximations for the distribution of the difference in binomial proportions. The assumed population proportion of impending relapse at or before 182 days for the oral aripiprazole (10 to 30 mg) was 18%, and the non-inferiority margin was 11.5%. The resulting sample size was 260 patients per arm for each of the IM depot 400/300mg and oral aripiprazole (10 to 30 mg) arms.

For the superiority comparison of IM depot 400/300mg to IM depot 50/25mg, on a 2:1 randomization, sample sizes of 260 and 130, respectively, provide about 95% power at alpha=0.05 (two-sided). A difference of 17% is assumed. In total, 650 subjects were estimated to be randomized.

Randomisation

Stabilised patients with oral aripiprazole were randomized to double-blind treatment on the day that the week 8 was fulfilled via an IVRS (Interactive voice response system) and/or an interactive web response (IWR) system. Subjects were randomized 2:2:1 to one of 3 respective treatment groups, stratified by region (US and non-US). In addition, each subject randomized to oral aripiprazole was

randomly assigned to a placebo group to match the administration procedure for either the aripiprazole IM depot 400 mg/300 mg group or the aripiprazole IM depot 50 mg/25 mg group.

Blinding (masking)

The investigator was blinded both to treatment (active vs placebo) and to dose of aripiprazole IM depot (400 mg vs 50 mg vs placebo). Aripiprazole IM depot formulation could not be blinded, an unblinded Site Study Drug Manager (USSDM) dispensed open-label and double-blind oral trial medication at weekly and biweekly visits, as directed by the IVRS/IWR, and administered all IM depot injections. This individual was utilized to maintain the blind for site staff involved with trial assessments. Subjects randomized to either dose of aripiprazole IM depot (400 mg or 50 mg) continued to receive oral aripiprazole 10 mg to 20 mg daily (dispensed as double-blind trial medication) for the first 14 days of maintenance phase in order to maintain therapeutic plasma concentrations.

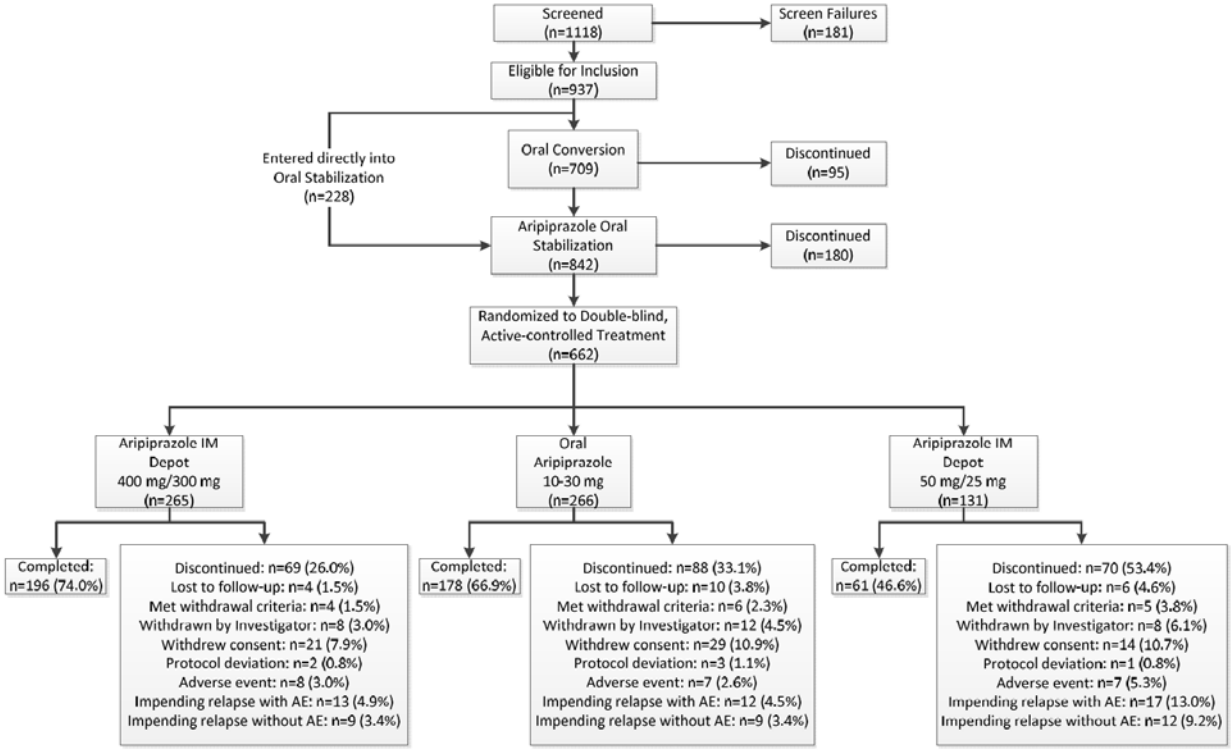
Statistical methods

Primary Efficacy Analysis: all subjects belonging to the ITT dataset were included. The test of non-inferiority of aripiprazole IM depot (400 mg/300 mg) to oral aripiprazole (10 to 30 mg) was performed using a 95% confidence interval (CI; 2-sided) for the difference in the estimated proportion of subjects meeting impending relapse criteria by end of Week 26 (aripiprazole IM depot 400 mg/300 mg vs oral aripiprazole tablets 10 mg to 30 mg). Non-inferiority was considered confirmed if the upper bound of the 2-sided 95% CI was below the predefined margin, 11.5%. Once non-inferiority was declared by the preceding test, superiority of IM depot 400 mg/300 mg over IM depot 50 mg/25 mg was tested by examining the difference in the estimated proportions of subjects meeting impending relapse criteria between IM depot 400 mg/300 mg and IM depot 50 mg/25 mg by end of Week 26 using z-statistic for statistical significance at the 0.05 significance level (2-sided) as assay sensitivity analysis. In addition, a similar test was performed to compare oral aripiprazole tablets 10-30 mg with aripiprazole IM depot 50 mg/25 mg. Although the primary efficacy analysis was based on the ITT population, a similar analysis for the primary efficacy endpoint was also performed by excluding subjects who were unblinded or potentially unblinded at site level and excluding duplicate-entry subjects with overlapping aripiprazole oral tablets/IM depot injections.

Secondary Efficacy Analysis: The Cox Proportional Hazard model in the model was fitted to the time to impending relapse event data with treatment as factor. The 95% CIs for the hazard ratios (aripiprazole IM depot 400 mg/300 mg to oral aripiprazole, aripiprazole IM depot 400 mg/300 mg to aripiprazole IM depot 50 mg/25 mg) were provided. The log-rank test was performed to test the equality of survival curves (aripiprazole IM depot 400 mg/300 mg vs aripiprazole IM depot 50 mg/25 mg) at the 0.05 significance level (2-sided). Percentage of patients (with impending relapse as per criteria, responders, achieving remission) was analysed using Chi-squared tests. Descriptive statistics for other variables (e.g mean changes from baseline for PANSS total score, CGI-S, PANSS positive and negative subscales, mean CGI-I score) were also used with analysis using covariance (ANCOVA) model or Cochran-Mantel-Haenszel method. Additionally, changes from baseline in PANSS total score and CGI-S score were analyzed using the Mixed Model Repeated Measures (MMRM) model and OC datasets. Kaplan-Meier curves for the time to discontinuation due to all causes were plotted and analyzed using the log-rank test. In order to assess sensitivity of results due to missing data, analyses were performed using both LOCF and OC methods. The LOCF method was used to impute the missing data at post-baseline visits in the stabilisation and maintenance phases for the efficacy analysis.

2.5.2.2. Results

Participant flow- Figure 4



Recruitment

Study period was from 26 September 2008 to 31 August 2012.

Conduct of the study

Three protocol amendments were made. These were related to study design and evaluation (mainly safety). Out of these amendments, a main change related to the primary efficacy endpoint was made from “time from randomization to exacerbation of psychotic symptoms/impending relapse in Phase 3” to “the proportion of subjects experiencing exacerbation of psychotic symptoms/impending relapse by end of 26 weeks of treatment from the date of randomization in Phase 3, in schizophrenic subjects who have maintained stability on oral aripiprazole for at least 8 consecutive weeks in Phase 2 of the study.” The original primary efficacy endpoint, “time to exacerbation of psychic symptoms/impending relapse” became, under this amendment, a secondary efficacy endpoint. The statistical method was consequently amended considering this change.

Overall, 8 subjects discontinued due to protocol deviations: 2 during the stabilisation phase and 6 during the maintenance phase. The proportion of patients was 2(0.8%) in the IM aripiprazole depot 400mg/300mg group, 3 (1.1%) in the oral aripiprazole 10-30 mg group and 1 (0.8%) in the IM aripiprazole depot 50 mg/25 mg.

Number analysed

During the study, 12 subjects were identified as either enrolled at 2 different study sites or enrolled in another trial investigating aripiprazole IM depot (Trial 31-07-246 or Trial 31-08-248). There were also 13 confirmed individual subject unblindings during the course of the study, including 2 intentional and 11 unintentional unblindings. Efficacy analysis was conducted including and excluding these patients. A total of 662 patients were randomised: 265/662 in Aripiprazole IM (400/300mg) arm, 266/662 in Aripiprazole oral (10-30 mg) arm, and 131/662 in Aripiprazole IM (50/25mg) arm. Completers in each arm were: 196/662 in Aripiprazole IM (400/300), 178/662 in Aripiprazole oral (10-30 mg), and 61/662 in Aripiprazole IM (50/25mg).

Baseline data

These are presented in Tables 3 and 4.

Table 3 Demographic characteristics in the Maintenance Phase (Randomised Subjects)

Demographic Characteristic	Aripiprazole IM Depot 400 mg/300 mg (N = 265)	Oral Aripiprazole 10-30 mg (N = 266)	Aripiprazole IM Depot 50 mg/25 mg (N = 131)	Total (N = 662)
Sex, n (%)				
Male	160 (60.4)	168 (63.2)	78 (59.5)	406 (61.3)
Female	105 (39.6)	98 (36.8)	53 (40.5)	256 (38.7)
Age (years)				
Mean (SD)	41.7 (10.4)	41.2 (10.8)	40.2 (9.6)	41.2 (10.4)
Range	18-60	18-60	21-59	18-60
< 45	150 (56.6)	146 (54.9)	84 (64.1)	380 (57.4)
≥ 45	115 (43.4)	120 (45.1)	47 (35.9)	282 (42.6)
Weight (kg)				
Mean (SD)	83.40 (20.90)	83.70 (19.20)	82.90 (24.40)	83.40 (21.00)
Range	47.70-164.20	48.00-150.00	42.20-201.80	42.20-201.80
Height (cm)				
Mean (SD)	169.7 (9.9)	170.7 (9.8)	169.9 (9.9)	170.1 (9.9)
Range	135.0-194.0	149.0-194.0	149.0-208.0	135.0-208.0
BMI (kg/m^2)				
Mean (SD)	28.9 (6.7)	28.7 (5.9)	28.7 (7.9)	28.8 (6.7)
Range	17.8-53.9	18.4-53.9	17.3-57.6	17.3-57.6
≤ 28	141 (53.2)	136 (51.1)	70 (53.4)	347 (52.4)
> 28	124 (46.8)	130 (48.9)	61 (46.6)	315 (47.6)
Race, n (%)				
Caucasian	160 (60.4)	153 (57.5)	74 (56.5)	387 (58.5)
Black or African American	56 (21.1)	64 (24.1)	33 (25.2)	153 (23.1)
American Indian or Alaska Native	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Asian	29 (10.9)	26 (9.8)	14 (10.7)	69 (10.4)
Other	20 (7.5)	22 (8.3)	10 (7.6)	52 (7.9)
Ethnicity, n (%)				
Hispanic/Latino	49 (18.5)	35 (13.2)	14 (10.7)	98 (14.8)
Non-Hispanic/Latino	216 (81.5)	231 (86.8)	117 (89.3)	564 (85.2)
Region, n (%)				
US	97 (36.6)	98 (36.8)	48 (36.6)	243 (36.7)
Non-US	168 (63.4)	168 (63.2)	83 (63.4)	419 (63.3)

Source: CT-3.1.2

Table 4 Baseline Disease Severity in the Maintenance Phase (Randomised Subjects)

Baseline Characteristic	Aripiprazole IM Depot 400 mg/300 mg (N = 265)	Oral Aripiprazole 10-30 mg (N = 266)	Aripiprazole IM Depot 50 mg/25 mg (N = 131)	Total (N = 662)
Age at first diagnosis of schizophrenia (years)				
Mean (SD)	28.2 (9.3)	26.9 (9.1)	26.3 (7.9)	27.3 (9.0)
Range	13-55	8-50	12-51	8-55
PANSS total score				
Mean (SD)	58.0 (12.9)	56.6 (12.7)	56.1 (12.6)	57.1 (12.8)
Range	30-80	30-79	30-80	30-80
Conceptual Disorganization (P2)				
Mean (SD)	2.0 (0.9)	2.0 (0.9)	1.9 (0.9)	2.0 (0.9)
Range	1-4	1-4	1-4	1-4
Suspiciousness (P6)				
Mean (SD)	2.3 (1.0)	2.2 (0.9)	2.1 (1.0)	2.2 (1.0)
Range	1-4	1-4	1-4	1-4
Hallucinatory (P3)				
Mean (SD)	1.9 (1.1)	1.7 (1.0)	1.6 (0.9)	1.8 (1.0)
Range	1-4	1-4	1-4	1-4
Unusual Thought Content (G9)				
Mean (SD)	2.1 (0.9)	1.9 (0.9)	2.0 (0.9)	2.0 (0.9)
Range	1-4	1-4	1-5	1-5
CGI Severity Score				
Mean (SD)	3.1 (0.7)	3.1 (0.8)	3.0 (0.8)	3.1 (0.8)
Range	1-4	1-4	1-4	1-4
CGI Improvement Score[a]				
Mean (SD)	3.2 (0.9)	3.3 (0.9)	3.1 (1.0)	3.2 (0.9)
Range	1-5	1-6	1-5	1-6
CGI-SS Severity Score				
Mean (SD)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)
Range	1-2	1-2	1-2	1-2
CGI-SS Change Score[a]				
Mean (SD)	4.0 (0.2)	4.0 (0.1)	4.0 (0.3)	4.0 (0.2)
Range	2-5	3-4	1-4	1-5
Outpatient status				
Yes	265 (100.0)	266 (100.0)	131 (100.0)	662 (100.0)

Outcomes and estimation

Data are presented in Tables 5, 6 and Figure 5.

Table 5 Analysis of estimated proportion of subjects with impending relapse by week 26 – primary endpoint results (DB, active controlled phase efficacy sample)

Test	Double-blind, Active-controlled Phase Treatment	Number of Randomized Subjects	Number of Relapsed Subjects[a]	Overall Relapse Rate (%)[a]	Week 26			
					Estimated Relapse Rate (%) (SE)[b]	Difference (%)[c]	95% CI	P-value[d]
Non-inferiority	Aripiprazole IM depot 400 mg/300 mg	265	22	8.30	7.12 (1.62)	−0.64	−5.26, 3.99	0.7871
	Oral Aripiprazole 10-30 mg	266	21	7.89	7.76 (1.72)			
Superiority[e]	Aripiprazole IM depot 400 mg/300 mg	265	22	8.30	7.12 (1.62)	−14.68	−23.09, −6.27	0.0006
	Aripiprazole IM depot 50 mg/25 mg	131	29	22.14	21.80 (3.97)			

Note: Definition of impending relapse is provided in Section 2.2.

[a]The summary statistics are based on all available relapse data for all subjects in the efficacy sample.

[b]Relapse rates are estimated from the Kaplan-Meier curves for time to impending relapse at Day 182 (Week 26) and SEs were calculated using Greenwood's formula.

[c]Difference = estimated relapse rate for aripiprazole IM depot 400 mg/300 mg group minus estimated relapse rate for the oral aripiprazole tablets 10-30 mg group in the non-inferiority test, or aripiprazole IM depot 50 mg/25 mg in the superiority test.

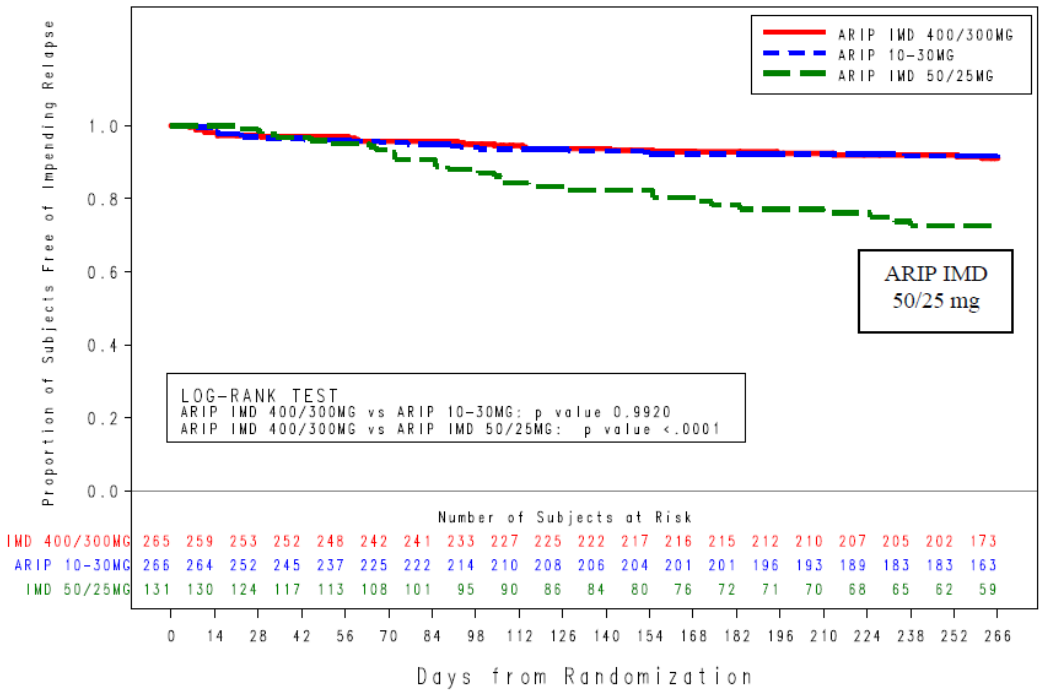
[d]P-values were derived using z-statistics.

[e]Superiority comparison was done to test assay sensitivity for the non-inferiority study design.

Source: CT-5.1.1

Further substantiation of assay sensitivity was provided by the demonstration that the difference (−14.04%) between oral aripiprazole tablets 10-30 mg and aripiprazole IM depot 50 mg/25 mg in estimated proportion of subjects experiencing impending relapse by end of Week 26 was statistically significant in favor of oral aripiprazole tablets (p = 0.0012).

Figure 5. Kaplan-Meier Product Limit Plot of Time to Impending Relapse (DB, active controlled phase efficacy sample)- Secondary endpoint results



ARIP: aripiprazole, IMD= IM depot

Table 6. Mean Change from baseline to week 38 for other secondary efficacy variables – Secondary efficacy results

Parameter	Visit	LS Mean (SE)[a] Change From Baseline			Comparison Arip IM depot 400/300 mg vs Oral Arip		Comparison Arip IM depot 400/300 mg vs Arip IM depot 50/25 mg	
		Arip IM depot 400/300 mg (N = 265)	Oral Arip 10-30 mg (N = 266)	Arip IM depot 50/25 mg (N = 131)	Difference 95% CI[a]	P-value[a]	Difference 95% CI[a]	P-value[a]
PANSS Total Score	Baseline[b]	57.94 (0.786) n = 263	56.57 (0.782) n = 266	56.08 (1.114) n = 131	1.37 (−0.81, 3.55)	0.2179	1.85 (−0.83, 4.53)	0.1751
	Week 38	−1.66 (0.718) n = 263	0.58 (0.714) n = 266	3.08 (1.017) n = 131	−2.24 (−4.23, −0.25)	0.0272	−4.74 (−7.19, −2.30)	0.0002
PANSS Positive Subscale Score	Baseline[b]	12.76 (0.230) n = 263	12.15 (0.228) n = 266	11.80 (0.326) n = 131	0.60 (−0.03, 1.24)	0.0634	0.96 (0.17, 1.74)	0.0168
	Week 38	−0.12 (0.249) n = 263	0.52 (0.247) n = 266	1.46 (0.352) n = 131	−0.64 (−1.33, 0.05)	0.0675	−1.58 (−2.43, −0.73)	0.0003
PANSS Negative Subscale Score	Baseline[b]	16.79 (0.312) n = 263	16.93 (0.310) n = 266	17.10 (0.442) n = 131	−0.14 (−1.00, 0.73)	0.7544	−0.31 (−1.37, 0.75)	0.5689
	Week 38	−0.74 (0.220) n = 263	−0.15 (0.219) n = 266	−0.19 (0.312) n = 131	−0.59 (−1.20, 0.02)	0.0572	−0.56 (−1.31, 0.19)	0.1449
CGI-S	Baseline[b]	3.12 (0.050) n = 259	3.09 (0.049) n = 263	2.95 (0.071) n = 129	0.02 (−0.11, 0.16)	0.7262	0.16 (−0.01, 0.33)	0.0605
	Week 38	−0.13 (0.049) n = 259	0.05 (0.049) n = 263	0.23 (0.070) n = 129	−0.17 (−0.31, −0.04)	0.0123	−0.36 (−0.52, −0.19)	< 0.0001
CGI-I[c]	Week 38	3.27 (1.16) n = 263	3.66 (1.16) n = 266	4.02 (1.32) n = 131	NA	0.0002	NA	< 0.0001

Arip = aripiprazole; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; CI = Confidence Interval; Diff = difference; IM = intramuscular; LOCF = last observation carried forward; LS = least squares (mean); NA = Not applicable; PANSS = Positive and Negative Symptom Scale; SE = standard error

Note: Except for CGI-I, subjects with baseline and at least one postbaseline assessment are included. For CGI-I, subjects with at least one postbaseline assessment are included.

[a] The LS means (adjusted mean), SE, difference, 95% CIs, and p-values are derived from an analysis of variance model with treatment as term for the baseline value and an analysis of covariance model with treatment as term and baseline as covariate for change from baseline.

[b] Actual LS mean values and standard errors are shown for baseline.

[c] Mean values and standard deviations are shown for CGI-I.

The proportion of responders (ie, subjects who met the stability criteria) at endpoint double blind maintenance phase was 89.8% (237/264) in the aripiprazole IM depot 400 mg/300 mg group compared with 89.4% (235/263) in the oral aripiprazole 10-30 mg group, and 75.2% (97/129) in the aripiprazole IM depot 50 mg/25 mg group. There was no significant difference in the proportion of responders between the aripiprazole IM depot 400 mg/300 mg group and the oral aripiprazole 10-30 mg group (p = 0.8750); however, the proportion of responders was statistically significantly higher in

the aripiprazole IM depot 400 mg/300 mg group than in the aripiprazole IM depot 50 mg/25 mg group (p = 0.0001).

The proportion of subjects achieving remission was 48.8% (105/215) in the aripiprazole IM depot 400 mg/300 mg group compared with 53.2% (107/201) in the oral aripiprazole 10-30 mg group, and 59.7% (43/72) in the aripiprazole IM depot 50 mg/25 mg group. The differences between the aripiprazole IM depot 400 mg/300 mg group and oral aripiprazole 10-30 mg group, and between the aripiprazole IM depot 400 mg/300 mg and aripiprazole IM depot 50 mg/25 mg groups were not statistically significant (p = 0.3700 and p = 0.1097, respectively).

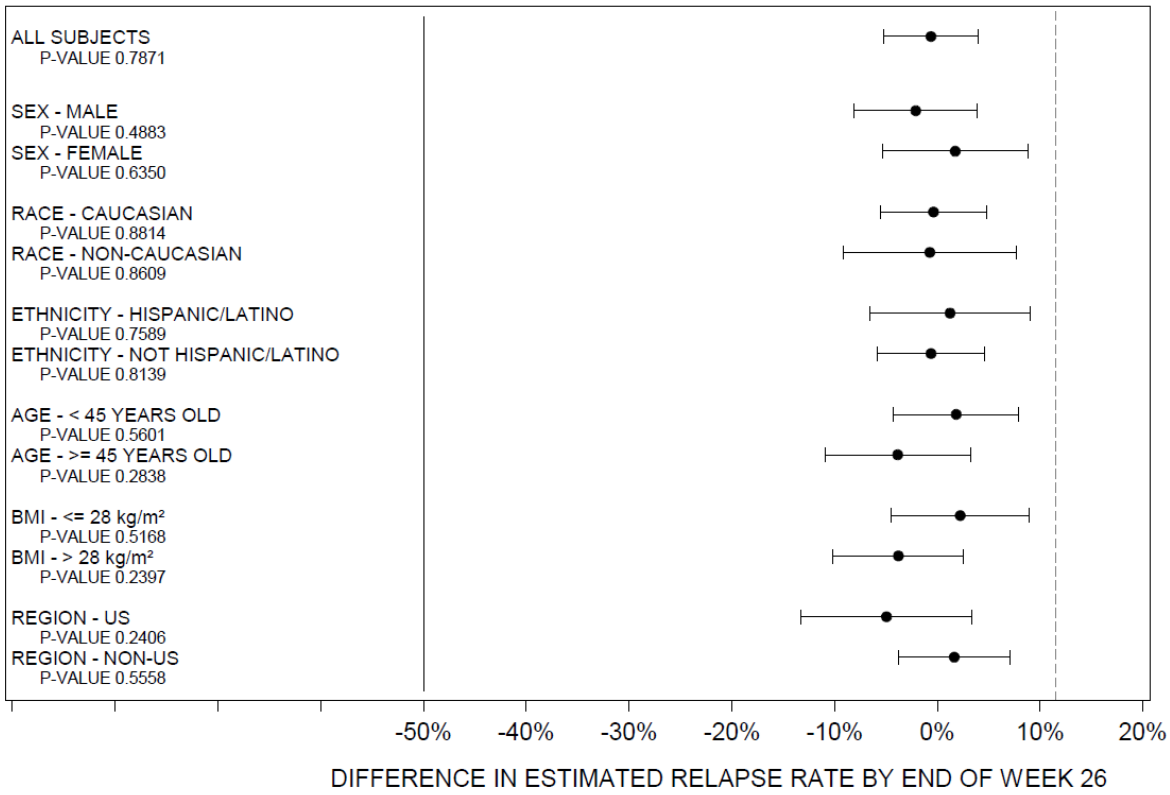
Sixty seven (67/265, 25.3%) patients treated with IM aripiprazole 400mg/300 mg depot discontinued due to all causes by Day 280, as compared to 87 (87/266, 32.7%) in the oral aripiprazole 10-30 mg group, 266 subjects were randomly assigned to treatment in the Double blind, Active-controlled Phase; 87 discontinued by Day 280, for a discontinuation rate of 32.7%. There was a statistically significant difference in time to discontinuation due to all reasons between the 2 groups (log-rank test, p = 0.0484) in favor of the aripiprazole IM depot 400 mg/300 mg treatment group. In the aripiprazole IM depot 50 mg/25 mg group, 70 of the 131 subjects randomly assigned to treatment discontinued, for a discontinuation rate of 53.4%. The median time to discontinuation was 234 days and there was a statistically significant difference between the aripiprazole IM depot 400 mg/300 mg and the aripiprazole IM depot 50 mg/25 mg groups (p < 0.0001) in favor of the aripiprazole IM depot 400 mg/300 mg treatment group.

For subjects in the double blind maintenance phase, a 0.45 and 0.08 point increases for the aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg groups,were noted in the PSP total score, respectively. There was no significant difference in the magnitude of the change between the 2 treatment groups (p = 0.9946). However, for subjects in the aripiprazole IM depot 50 mg/25 mg group, the PSP total score decreased from baseline to the last visit during the double blind maintenance phase (-2.39 points), indicating a decrease in social functioning. The difference in the change from baseline to last visit in the PSP score was statistically significant between the aripiprazole IM depot 50 mg/25 mg group and the aripiprazole IM depot 400 mg/300 mg group (p = 0.0266).

2.5.2.3. Ancillary analyses

Data are presented in Figures 6 and 7 indicating no relevant differences in efficacy data among the analysed subgroups.

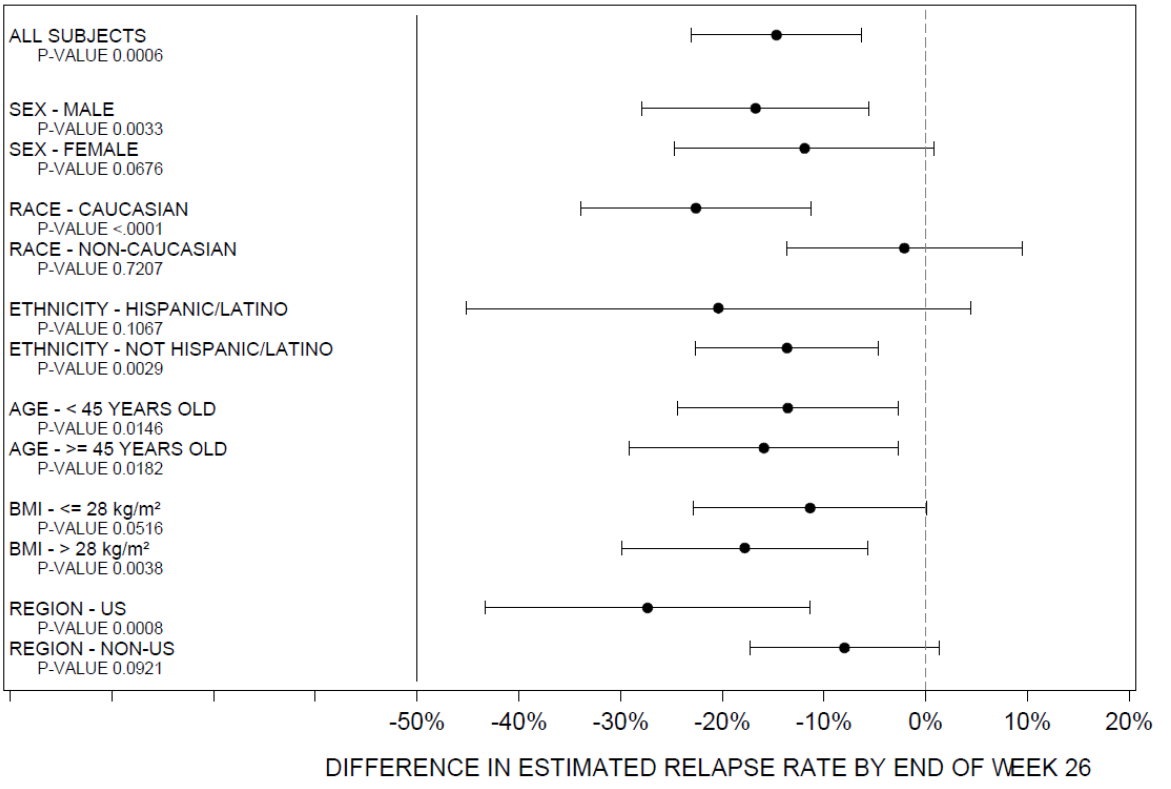
Figure 6 Difference and 95% confidence intervals in estimated proportion of subjects with impending relapse by end of week 26 between IM aripiprazole depot 400 mg/300 mg group and oral aripiprazole 10-30 mg (DB, active controlled phase efficacy sample)



Note : reference line for predefined non inferiority margin 11.5% (dotted)

Figure 2.7.3.3.3.1-1 Difference and 95% Confidence Intervals in Estimated Proportion of Subjects with Impending Relapse by End of Week 26 Between Aripiprazole IM Depot 400 mg/300 mg Group and Oral Aripiprazole Tablets 10-30 mg (Trial 31-07

Figure 7 Difference and 95% confidence intervals in estimated proportion of subjects with impending relapse by end of week 26 between IM aripiprazole depot 400 mg/300 mg group and aripiprazole IM depot 50 mg/25 mg group (DEL, active-controlled phase efficacy sample)



Differences <0% favour aripiprazole IM depot 400 mg/300 mg

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7 Summary of efficacy for trial 31-07-247

Title: Study 31-07-247				
Study identifier	31-07-247			
Design	Multinational, phase 3, Randomized (2:2:1),double-blind, activecontrolled, parallel arms, Prior to entry subjects were required to be clinically stable on oral aripiprazole for 8 consecutive weeks			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8 to 28 (oral stabilization) + 38 weeks (maintenance) 6+6 (screening period + conversion to oral aripiprazole) trial 31-08-248: 52 weeks + trial 31-08-270 (anticipated end of trial by December 2018)	
Hypothesis	Non-inferiority			
Treatments groups	Aripiprazole IM (400/300 mg)		IM depot, 265 randomised	
	Aripiprazole oral (10-30mg)		Oral tablets, 266 randomised	
	Aripiprazole IM (50/25 mg) (pseudo-placebo)		IM depot, 26 weeks, 131 randomised	
Endpoints and definitions	Primary endpoint	Estimated impending relapse rate as per the definition of this term	The primary endpoint of this trial was the estimated proportion of subjects experiencing impending relapse by end of 26 weeks of treatment from the date of randomization in the Double-blind, Active-controlled Phase, in subjects with schizophrenia who had maintained stability on oral aripiprazole for at least 8 consecutive weeks in the Oral Stabilization Phase of the trial before the first monthly IM injection	
	Secondary endpoint	1-Time to impending relapse	Time to impending relapse from the date of randomization in the Double-blind, Active controlled Phase	
Database lock	Performed per GCP on 15 May 2012 (for all but 9 subjects continuing in safety follow-up) and on 28 September 2012 for the remaining 9 subjects.			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat time point: end of 26 weeks of treatment from the date of randomization			
Descriptive statistics and estimate variability	Treatment group	Aripiprazole IM (400/300 mg)	Aripiprazole oral (10-30mg)	Aripiprazole IM (50/25 mg) (pseudo-placebo)

	Number of subject	265	266	131
	Estimated impending relapse rate %	7.12	7.76	21.80
	SE	1.62	1.72	3.97

Effect estimate per comparison	Primary endpoint	Comparison groups	Aripiprazole IM (400/300 mg) vs. Aripiprazole oral (10-30mg)
		Difference between groups %	-0.6
		95%CI	-5.26, 3.99
		P-value (z-stats)	0.7871
	Primary endpoint	Comparison groups	Aripiprazole IM (400/300 mg) vs. Aripiprazole IM (50/25 mg) (pseudo-placebo)
		Difference %	-14.7
		95%CI	-23.09, -6,27
		P-value (z-stats)	0.0006
Notes	The objective of the primary efficacy analysis was to demonstrate non-inferiority of aripiprazole IM depot400 mg/300 mg to oral aripiprazole tablets 10-30 mg with regard to the primary efficacy endpoint. Other analysis excluding subjects who were unblinded or potentially unblinded at site level and excluding duplicate-entry subjects with overlapping aripiprazole oral tablets/IM depot injections revealed comparable data		

Descriptive statistics and estimate variability	Treatment group	Aripiprazole IM (400/300 mg)	Aripiprazole oral (10-30mg)	Aripiprazole IM (50/25 mg) (pseudo-placebo)
	Number of subject	265	266	131
	Time to impending relapse median HR	NA 1.009 3.158	NA 0.991	NA 0.317
	95%CI	0.555, 1834 1.813,5.502	0.545, 1.803	 0.182, 0.552

Effect estimate per comparison	Secondary endpoint	Comparison groups	Aripiprazole IM (400/300 mg) vs. Aripiprazole oral (10-30mg)
		HR	
		95%CI	
		p value Log-rank test	0.9920

	Secondary endpoint	Comparison groups	Aripiprazole IM (400/300 mg) vs. Aripiprazole IM (50/25 mg) (pseudo-placebo)
		HR	
		95%CI	
		p value Log-rank test	<0.0001

NA: not available

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

No analysis was performed across trials.

2.5.2.5. Clinical studies in special populations

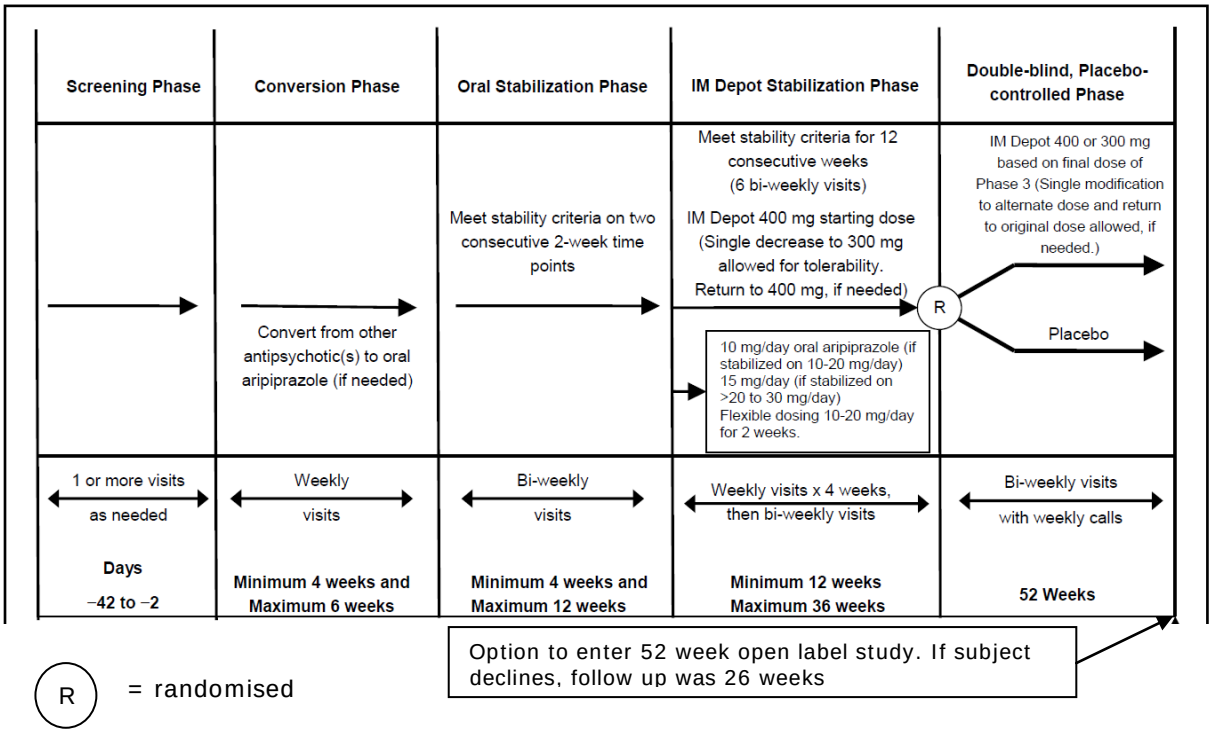
No trials with IM aripiprazole depot have been performed in any special schizophrenic patient populations.

2.5.2.6. Supportive studies

2.5.2.6.1. Study 31-07-246

Although the design of study 31-07-246 (see Figure 8) was different than the main study 31-07-247, as described above, the enrolled subject population, efficacy assessments, and criteria for stability and impending relapse were the same in these studies.

Figure 8

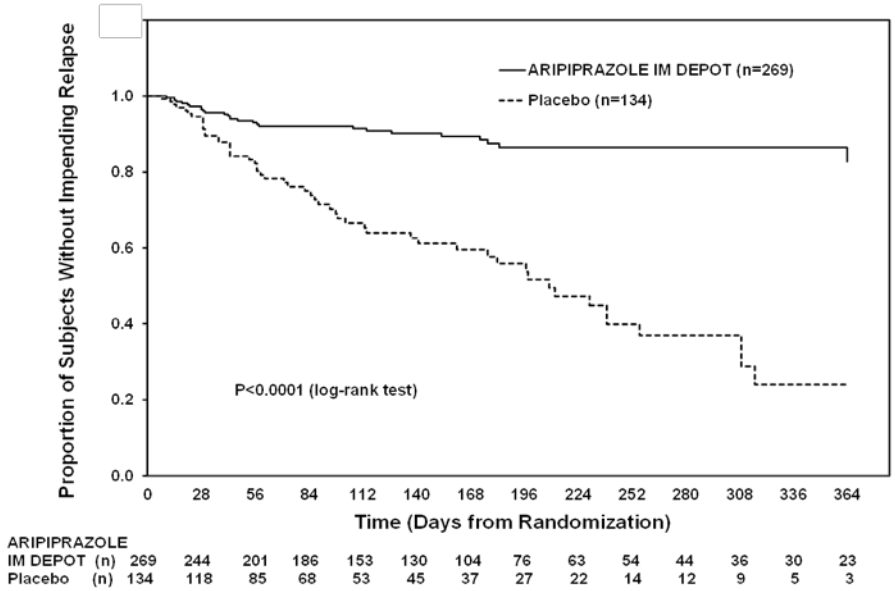


The primary efficacy endpoint was the time to impending relapse during the Double-blind, Placebo-controlled Phase. A prespecified interim efficacy analysis was performed and included 344 randomized subjects and 64 events of impending relapse. These interim data showed that time to impending

relapse was significantly shorter for subjects randomized to placebo compared with subjects randomized to aripiprazole IM depot 400 mg/300 mg in the double-blind, placebo-controlled Phase ($p < 0.0001$; log-rank test). The hazard ratio from the Cox proportional hazard model for the placebo to aripiprazole IM depot 400 mg/300 mg comparison was 4.72 (95% CI = 2.81, 7.94); thus, subjects in the placebo group had a 4.72-fold greater risk of experiencing impending relapse than subjects in the aripiprazole IM depot 400 mg/300 mg group. The hazard ratio from the Cox proportional hazard model for the aripiprazole IM depot 400 mg/300 mg to placebo comparison was 0.212 (95% CI = 0.126, 0.357).

The final efficacy analysis included 403 randomized subjects and 80 impending relapse events. Results from the final analysis were consistent with the interim analysis results showing that the time to impending relapse was significantly shorter for subjects in the placebo group compared with subjects in the aripiprazole IM depot 400 mg/300 mg group ($p < 0.0001$; log-rank test). The hazard ratio from the Cox proportional hazard model for the placebo to aripiprazole IM depot 400 mg/300 mg comparison was 5.029 (95% CI = 3.154, 8.018), thus subjects in the placebo group had a 5.03-fold greater risk of experiencing impending relapse than subjects in the aripiprazole IM depot 400 mg/300 mg group. The hazard ratio from the Cox proportional hazard model for the aripiprazole IM depot 400 mg/300 mg to placebo comparison was 0.199 (95% CI = 0.125, 0.317). See Figure 9.

Figure 9 Kaplan-Meier Product Limit Plot for Time to Exacerbation of Psychotic Symptoms/Impending Relapse



Additional efficacy analysis following the last dose in the oral stabilization phase was performed showing that the effect of IM aripiprazole depot was sustained up to 6 weeks (i.e., 2-week delay in dosing) in case of patients missing their doses.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

According to the CHMP guideline on clinical development on schizophrenia (EMA/CHMP/40072/2010 Rev. 1) which incorporated the existing CHMP appendix related to methodology of clinical trials

concerning the development of depot preparations of approved medicinal products in schizophrenia, depot preparations of antipsychotic products will usually be given after the patient is stabilised on the oral form. For the latter, efficacy and safety will have been shown in agreement with the existing guidance. This implies that not only the effect in short-term trials is known but shown that the effect of the product is maintained over time. The duration of the studies (more than 6 months double blind maintenance phase) were considered sufficient to support the claim for maintenance treatment in schizophrenia. The applicant followed this CHMP guideline and presented two efficacy studies aiming at demonstrating maintenance of the effect of the depot formulation (31-07-246, 31-07-247), as well as non-inferiority versus the oral formulation (31-07-247). According to the applicant, study 31-07-246 was conducted following recommendation from other regulatory authorities. Taking into account the design of study 31-07-246 that did not include a direct comparison with oral aripiprazole and used a different primary efficacy endpoint than study 31-07-247, the CHMP therefore considered the active controlled study 31-07-247 as the pivotal study. Study 31-07-246 is regarded as supportive of the present application.

In the study population, patients were stabilised on oral treatment before evaluating the efficacy of the depot formulation in maintenance treatment. The demographic characteristics for subjects randomized to the double blind maintenance phase were similar to those seen in the previous phases; most subjects randomized were male (406/662, 61.3%), Caucasian (387/662, 58.5%), and non-Hispanic/Latino (564/662, 85.2%). The percentages of Black or African American and Asian subjects were 23.1% (153/662 subjects) and 10.4% (69/662 subjects), respectively. The mean age was 41.2 years and mean BMI was 28.8 kg/m2 (ranged from 17.3 to 57.6 kg/m2). These baseline data were comparable across treatment groups. Whilst overall, the CHMP considered that the patients included in study 31-04-247 were sufficiently representative of the intended population (with inclusion of EU patients), the mean age (considered slightly higher than expected) and the long duration of the oral stabilisation (for at least 8 weeks) may have been possible factors contributing to the lower than anticipated relapse rate observed in both studies..

In study 31-07-247, the main protocol changes related to the primary efficacy endpoint was discussed during a CHMP scientific advice. Change from “time from randomization to exacerbation of psychotic symptoms/impending relapse in Phase 3” to “the proportion of subjects experiencing exacerbation of psychotic symptoms/impending relapse by end of 26 weeks of treatment from the date of randomization in Phase 3, in schizophrenic subjects who have maintained stability on oral aripiprazole for at least 8 consecutive weeks in Phase 2 of the study” was proposed due to the lower than the anticipated relapse rates observed during the study , the original primary efficacy endpoint, becoming a secondary efficacy endpoint. During this scientific advice, the CHMP considered that this change might require a further revision of the non inferiority margin of the IM depot (originally of 15%, considering 31% relapse rate), suggesting a lowering of the proposed 11.5% to 10% margin.

The initial indication applied for was: maintenance treatment of schizophrenia in adults. On the basis of the design of the presented efficacy studies, the CHMP recommended to change the indication to the following: “maintenance treatment of schizophrenia in adult patients stabilized with oral aripiprazole”. This was agreed by the applicant.

Efficacy data and additional analyses

In pivotal study 31-07-247, the objective of the primary efficacy analysis was to demonstrate non-inferiority of aripiprazole im depot 400 mg/300 mg to oral aripiprazole tablets 10-30 mg with regard to the primary efficacy endpoint “proportion of subjects experiencing impending relapse” and thereafter to show superiority of the im formulation over the pseudo placebo (aripiprazole im 50/25 mg) for assay sensitivity. The estimated relapse rate by end of Week 26 was 7.12% in the aripiprazole IM depot 400

mg/300 mg group and 7.76% in the oral aripiprazole tablets 10-30 mg group, a difference of −0.6%. The 95% CI (−5.26, 3.99) for the difference in the estimated proportion of subjects experiencing impending relapse by end of Week 26 excluded the predefined non-inferiority margin of 11.5%. Since the difference in relapse rate between IM formulation and the oral form of -0.6% in favour of the IM arm with a 95% CI ranging between -5.26 and 3.99 showed an upper bound of 4% for the difference between IM and oral formulation, the CHMP considered that non-inferiority was demonstrated. Even with a 10% margin, as suggested in the CHMP scientific advice, the actual results would still demonstrate non inferiority, the pre-specified non inferiority margin of 11.5% was therefore not further questioned by the CHMP. The estimated proportion of subjects experiencing impending relapse by end of Week 26 for the aripiprazole IM depot 400 mg/300 mg group was statistically significantly lower than that of the aripiprazole IM depot 50 mg/25 mg group (21.8%; p = 0.0006). Thus, superiority of aripiprazole IM depot 400 mg/300 mg over aripiprazole IM depot 50 mg/25 mg was considered established by the CHMP and the validity of the trial design ie the results were not due to lack of events and assay sensitivity was confirmed.

The secondary efficacy endpoint, time to impending relapse, was similar in the aripiprazole IM depot 400 mg/300 mg group as compared with the oral aripiprazole tablets 10-30 mg group (hazard ratio = 0.992, 95% CI = 0.545, 1.803). However, the time to impending relapse was statistically significantly delayed (ie, improved) in the aripiprazole IM depot 400 mg/300 mg group compared with the aripiprazole IM depot 50 mg/25 mg group (log-rank test, p < 0.0001). The aripiprazole IM depot 50 mg/25 mg group had a 3.158-fold higher risk of relapse than the aripiprazole IM depot 400 mg/300 mg group (95% CI = 1.813, 5.502). Other secondary results were also consistent with the primary efficacy analysis showing stabilisation of the psychotic symptoms in patients treated with IM aripiprazole depot 400mg/300 mg and suggesting that the lower dose was not efficacious in the proposed indication.

Moreover, the proportion of responders was statistically significantly higher in the aripiprazole IM depot 400 mg/300 mg group than in the aripiprazole IM depot 50 mg/25 mg group (p = 0.0001).

In the supportive study 31-07-246, the primary efficacy variable was the time to impending relapse in adult subjects with schizophrenia who maintained stability for at least 12 consecutive weeks on aripiprazole IM depot 400 mg/300 mg. Results showed that time to impending relapse was significantly shorter for subjects randomized to placebo compared with subjects randomized to aripiprazole IM depot 400 mg/300 mg in the double blind maintenance phase (p < 0.0001; log-rank test) further supporting the primary efficacy analysis.

Dosing recommendation

Based on the dosing regimens, the method of administration used and the results observed in the efficacy studies, the applicant proposed a starting and maintenance dose of 400 mg, to be administered monthly in the gluteal muscle, with possible lower maintenance dose of 300 mg based on individual patient tolerability. The first dose should be accompanied by 14 consecutive days of concurrent treatment with 10 mg to 20 mg of oral aripiprazole. On the basis that patients who will be switching to the IM depot can be stabilized to different doses of oral aripiprazole (ranging from 10-30 mg), the CHMP requested additional analyses to support such dosing recommendation. Simulations were provided and considered satisfactory by the CHMP. These included cases where patients were stabilized on 10 to 30 mg daily oral aripiprazole and continued with 10 mg (patients receiving 10 to 20 mg oral aripiprazole prior to IM depot initiation) or 15 mg (patients receiving 20 to 30 mg oral aripiprazole prior to IM depot initiation) oral aripiprazole for 2 weeks after IM depot administration. In addition, the applicant clarified that the proposed concomitant use of oral aripiprazole for 2 weeks after administration of the initial dose of aripiprazole IM depot was to maintain aripiprazole concentrations around predose IM depot aripiprazole concentrations given the known slow absorption of IM

aripiprazole depot from the site of administration and was not an additional oral loading dose. Overall, the initial proposed dosing recommendation was sufficiently justified and no change was proposed by the CHMP.

In addition, simulations and additional efficacy analyses (see study 31-07-246) were also provided to support dosing recommendation in case of missed doses and included scenarios with delays of varying duration in the timing of the 2nd, 3rd, 4th and 10th aripiprazole IM depot administrations occurred. Simulation data showed the following situations: 1) when the 2nd dose was delayed by 1 week (7 days), the median aripiprazole concentration was slightly below the threshold of the therapeutic window; 2) When the 3rd dose was delayed by 1 week, the median aripiprazole concentration did not drop below the threshold of the therapeutic window; 3) When the 4th (representing steady state) or the 10th aripiprazole IM depot doses were delayed by 2 weeks (14 days), the median aripiprazole concentrations did not drop below the threshold of the therapeutic window. In addition, the simulation analysis predicted that administration of aripiprazole IM depot without concomitant oral therapy during a 1-week (7 days) delay for Doses 2 and 3 and during a 2-week (14 days) delay for doses 4 and beyond would result in median aripiprazole concentrations above the therapeutic window after administration of aripiprazole IM depot. On this basis and considering the efficacy of IM aripiprazole depot was sustained up to 6 weeks (i.e., 2-week delay in dosing) in case of patients missing their doses in study 31-27-246, it can be recommended that when the monthly aripiprazole IM depot administration is delayed, it should be administered as soon as possible and concomitant oral aripiprazole dosing is not needed if the delay is no longer than 7 days for the 2nd and 3rd injections and 14 days for the 4th and subsequent aripiprazole IM depot injections. However, if aripiprazole IM depot injections are delayed beyond 7 days for Doses 2 and 3 and beyond 14 days for Doses 4 and beyond, then re-initiation of therapy is needed (i.e., concurrent oral administration of aripiprazole for 2 weeks with the aripiprazole IM Depot injection).

2.5.4. Conclusions on the clinical efficacy

The CHMP concluded that the efficacy in the maintenance treatment of schizophrenia in adults, stabilised with oral aripiprazole was demonstrated in the proposed dosing regimen for Abilify Maintena.

2.6. Clinical safety

The safety database presented in the dossier included the following datasets:1) completed phase III controlled trials (**31-07-246 and 31-07-247**) and 2) all trials (completed and ongoing) excluding trial 31-08-003 which is an ongoing, double blind trial.

Patient exposure

As of April 2012, 1,624 adult subjects with schizophrenia have been exposed to aripiprazole IM depot (15-400 mg). Additional subjects have been exposed to aripiprazole IM depot in an ongoing Japanese double-blind phase 3 trial (trial 031-08-003), but treatment remains blinded and therefore these data are not available at this time. Of the 1,624 adult subjects exposed to aripiprazole IM depot, 1,539 subjects have been treated with aripiprazole IM depot 400 mg/300 mg, 995 subjects have received at least 7 aripiprazole IM depot 400 mg/300 mg injections (ie, have been treated for at least 6 months), 784 subjects have received at least 13 injections (ie, have been treated for at least 12 months), and 244 subjects received at least 26 injections (ie, have been treated for 24 months).

Adverse events

The AE profile of IM aripiprazole depot in the analysed safety datasets is summarised in Tables 8 and 9.

Table 8. Treatment-emergent adverse events reported during double blind treatment phases for 1% or more subjects across groups (controlled trials)

System Organ Class MedDRA Preferred Term	Aripiprazole IM Depot 400 mg/300 mg (N = 534; PEY = 283.5)		Oral Aripiprazole 10-30 mg (N = 266; PEY = 154.1)		Aripiprazole IM Depot 50 mg/25 mg (N = 131; PEY = 67.8)		Placebo (N = 134; PEY = 43.0)	
	n (%)	n per 100 PEY	n (%)	n per 100 PEY	n (%)	n per 100 PEY	n (%)	n per 100 PEY
Any TEAE	389 (72.8)	137.2	213 (80.1)	138.3	106 (80.9)	156.3	83 (61.9)	192.8
Gastrointestinal Disorders								
Diarrhea	15 (2.8)	5.3	9 (3.4)	5.8	6 (4.6)	8.8	3 (2.2)	7.0
Dry mouth	6 (1.1)	2.1	5 (1.9)	3.2	0 (0.0)	0.0	0 (0.0)	0.0
Dyspepsia	6 (1.1)	2.1	4 (1.5)	2.6	2 (1.5)	2.9	1 (0.7)	2.3
Nausea	10 (1.9)	3.5	4 (1.5)	2.6	3 (2.3)	4.4	2 (1.5)	4.6
Toothache	14 (2.6)	4.9	13 (4.9)	8.4	3 (2.3)	4.4	3 (2.2)	7.0
Vomiting	12 (2.2)	4.2	4 (1.5)	2.6	1 (0.8)	1.5	3 (2.2)	7.0
General Disorders and Administration Site Conditions								
Fatigue	11 (2.1)	3.9	9 (3.4)	5.8	2 (1.5)	2.9	1 (0.7)	2.3
Injection site induration	8 (1.5)	2.8	2 (0.8)	1.3	0 (0.0)	0.0	0 (0.0)	0.0
Injection site pain	**28 (5.2)**	**9.9**	**6 (2.3)**	**3.9**	**1 (0.8)**	**1.5**	**5 (3.7)**	**11.6**
Pyrexia	7 (1.3)	2.5	1 (0.4)	0.6	2 (1.5)	2.9	2 (1.5)	4.6
Infections and Infestations								
Bronchitis	7 (1.3)	2.5	5 (1.9)	3.2	5 (3.8)	7.4	2 (1.5)	4.6
Influenza	16 (3.0)	5.6	11 (4.1)	7.1	7 (5.3)	10.3	2 (1.5)	4.6
Nasopharyngitis	**31 (5.8)**	**10.9**	**25 (9.4)**	**16.2**	**9 (6.9)**	**13.2**	**7 (5.2)**	**16.3**
Upper respiratory tract infection	25 (4.7)	8.8	11 (4.1)	7.1	5 (3.8)	7.4	3 (2.2)	7.0
Injury, Poisoning and Procedural Complications								
Muscle strain	6 (1.1)	2.1	1 (0.4)	0.6	2 (1.5)	2.9	0 (0.0)	0.0
Investigations								
Blood creatine phosphokinase increased	10 (1.9)	3.5	6 (2.3)	3.9	5 (3.8)	7.4	2 (1.5)	4.6
Blood insulin increased	7 (1.3)	2.5	5 (1.9)	3.2	2 (1.5)	2.9	1 (0.7)	2.3
Blood pressure increased	6 (1.1)	2.1	1 (0.4)	0.6	0 (0.0)	0.0	3 (2.2)	7.0
Weight decreased	**35 (6.6)**	**12.3**	**16 (6.0)**	**10.4**	**12 (9.2)**	**17.7**	**4 (3.0)**	**9.3**

System Organ Class MedDRA Preferred Term	Aripiprazole IM Depot 400 mg/300 mg (N = 534; PEY = 283.5)		Oral Aripiprazole 10-30 mg (N = 266; PEY = 154.1)		Aripiprazole IM Depot 50 mg/25 mg (N = 131; PEY = 67.8)		Placebo (N = 134; PEY = 43.0)	
	n (%)	n per 100 PEY	n (%)	n per 100 PEY	n (%)	n per 100 PEY	n (%)	n per 100 PEY
Weight increased	**50 (9.4)**	**17.6**	**35 (13.2)**	**22.7**	**7 (5.3)**	**10.3**	**13 (9.7)**	**30.2**
Metabolism and Nutrition Disorders								
Decreased appetite	6 (1.1)	2.1	1 (0.4)	0.6	3 (2.3)	4.4	0 (0.0)	0.0
Diabetes mellitus	6 (1.1)	2.1	2 (0.8)	1.3	0 (0.0)	0.0	0 (0.0)	0.0
Musculoskeletal and Connective Tissue Disorders								
Arthralgia	15 (2.8)	5.3	4 (1.5)	2.6	0 (0.0)	0.0	1 (0.7)	2.3
Back pain	16 (3.0)	5.6	14 (5.3)	9.1	15 (11.5)	22.1	3 (2.2)	7.0
Muscle spasms	7 (1.3)	2.5	4 (1.5)	2.6	1 (0.8)	1.5	1 (0.7)	2.3
Musculoskeletal pain	6 (1.1)	2.1	4 (1.5)	2.6	2 (1.5)	2.9	1 (0.7)	2.3
Musculoskeletal stiffness	7 (1.3)	2.5	4 (1.5)	2.6	1 (0.8)	1.5	2 (1.5)	4.6
Pain in extremity	11 (2.1)	3.9	7 (2.6)	4.5	2 (1.5)	2.9	6 (4.5)	13.9
Nervous System Disorders								
Akathisia	**43 (8.1)**	**15.2**	**18 (6.8)**	**11.7**	**11 (8.4)**	**16.2**	**8 (6.0)**	**18.6**
Dizziness	14 (2.6)	4.9	6 (2.3)	3.9	2 (1.5)	2.9	4 (3.0)	9.3
Dyskinesia	8 (1.5)	2.8	2 (0.8)	1.3	1 (0.8)	1.5	1 (0.7)	2.3
Extrapyramidal disorder	7 (1.3)	2.5	2 (0.8)	1.3	0 (0.0)	0.0	0 (0.0)	0.0
Headache	**42 (7.9)**	**14.8**	**30 (11.3)**	**19.5**	**7 (5.3)**	**10.3**	**7 (5.2)**	**16.3**
Sedation	13 (2.4)	4.6	3 (1.1)	1.9	1 (0.8)	1.5	1 (0.7)	2.3
Somnolence	14 (2.6)	4.9	12 (4.5)	7.8	2 (1.5)	2.9	1 (0.7)	2.3
Tremor	24 (4.5)	8.5	9 (3.4)	5.8	6 (4.6)	8.8	2 (1.5)	4.6
Psychiatric Disorders								
Agitation	9 (1.7)	3.2	2 (0.8)	1.3	0 (0.0)	0.0	3 (2.2)	7.0
Anxiety	**35 (6.6)**	**12.3**	**13 (4.9)**	**8.4**	**10 (7.6)**	**14.7**	**10 (7.5)**	**23.2**
Depression	7 (1.3)	2.5	3 (1.1)	1.9	0 (0.0)	0.0	3 (2.2)	7.0
Insomnia	**58 (10.9)**	**20.5**	**37 (13.9)**	**24.0**	**18 (13.7)**	**26.5**	**12 (9.0)**	**27.9**
Psychotic disorder	16 (3.0)	5.6	8 (3.0)	5.2	8 (6.1)	11.8	9 (6.7)	20.9
Restlessness	16 (3.0)	5.6	4 (1.5)	2.6	4 (3.1)	5.9	3 (2.2)	7.0
Schizophrenia	10 (1.9)	3.5	5 (1.9)	3.2	10 (7.6)	14.7	5 (3.7)	11.6
Reproductive System and Breast Disorders								
Erectile dysfunction	6 (1.1)	2.1	1 (0.4)	0.6	1 (0.8)	1.5	0 (0.0)	0.0
Respiratory, Thoracic and Mediastinal Disorders								
Cough	14 (2.6)	4.9	7 (2.6)	4.5	5 (3.8)	7.4	4 (3.0)	9.3
Oropharyngeal pain	8 (1.5)	2.8	4 (1.5)	2.6	0 (0.0)	0.0	1 (0.7)	2.3
Vascular Disorders								
Hypertension	7 (1.3)	2.5	4 (1.5)	2.6	4 (3.1)	5.9	3 (2.2)	7.0

Abbreviations: AE = adverse event; IM = intramuscular; MedDRA = Medical Dictionary for Regulatory Activities; PEY = patient-exposure years; TEAE = treatment-emergent adverse event.

Note: TEAE was defined as an AE which started after commencement of randomized, double-blind trial medication, or an event that continued from baseline or from the end of the specific previous other treatment period, and became serious, worsening, trial medication-related, or resulted in death, discontinuation, interruption, or reduction of trial medication during the current treatment period. Subjects with multiple occurrences of TEAEs are counted only once per specific category.

Note: **Bolded** events were reported for ≥ 5% subjects in the aripiprazole IM depot 400 mg/300 mg group.

Source: SCS CT-2.4.2.2.1 and SCS CT-2.4.2.4.3.

Table 9.Treatment emergent adverse events reported for 5% or more subjects in any aripiprazole IM dosage category (all trials)

System Organ Class MedDRA Preferred Term	Aripiprazole IM Depot < 300 mg (N = 168; PEY = 72.4)		Aripiprazole IM Depot 300-400 mg (N = 1539; PEY = 1617.3)		Total (N = 1624; PEY = 1689.6)	
	n (%)	n per 100 PEY	n (%)	n per 100 PEY	n (%)	n per 100 PEY
Any TEAE	136 (81.0)	188.0	1105 (71.8)	68.3	1193 (73.5)	70.6
General Disorders and Administration Site Conditions						
Injection site pain	5 (3.0)	6.9	108 (7.0)	6.7	113 (7.0)	6.7
Infections and Infestations						
Nasopharyngitis	15 (8.9)	20.7	115 (7.5)	7.1	128 (7.9)	7.6
Upper respiratory tract infection	6 (3.6)	8.3	84 (5.5)	5.2	90 (5.5)	5.3
Investigations						
Blood creatine phosphokinase increased	10 (6.0)	13.8	27 (1.8)	1.7	36 (2.2)	2.1
Weight decreased	12 (7.1)	16.6	61 (4.0)	3.8	73 (4.5)	4.3
Weight increased	10 (6.0)	13.8	119 (7.7)	7.4	129 (7.9)	7.6
Musculoskeletal and Connective Tissue Disorders						
Back pain	16 (9.5)	22.1	68 (4.4)	4.2	82 (5.0)	4.9
Nervous System Disorders						
Akathisia	14 (8.3)	19.3	109 (7.1)	6.7	120 (7.4)	7.1
Headache	14 (8.3)	19.3	147 (9.6)	9.1	161 (9.9)	9.5
Psychiatric Disorders						
Anxiety	13 (7.7)	18.0	136 (8.8)	8.4	149 (9.2)	8.8
Insomnia	22 (13.1)	30.4	169 (11.0)	10.4	188 (11.6)	11.1
Psychotic disorder	9 (5.4)	12.4	60 (3.9)	3.7	67 (4.1)	4.0
Schizophrenia	12 (7.1)	16.6	47 (3.1)	2.9	58 (3.6)	3.4

Abbreviations: AE = adverse event; IM = intramuscular; MedDRA = Medical Dictionary for Regulatory Activities; PEY = patient-exposure years; TEAE = treatment-emergent adverse event.

Note: TEAE was defined as an AE which started after commencement of aripiprazole IM depot injection, or an event that continued from baseline or from the end of the specific previous other treatment period, and became serious, worsening, trial medication-related, or resulted in death, discontinuation, interruption, or reduction of trial medication during the current treatment period. Subjects with multiple occurrences of TEAEs are counted only once per specific category.

Note: 83 subjects received aripiprazole IM depot 50 mg/25 mg in Trial 31-07-247 and also received aripiprazole IM depot 400 mg/300 mg in Trial 31-08-248; these subjects are counted once in the total (aripiprazole IM depot 15-400 mg) column.

Treatment-emergent AEs potentially related to trial medication reported for ≥ 5% and < 10% of aripiprazole IM depot 400 mg/300 mg subjects were increased weight (48/534, 9.0%), akathisia (42/534, 7.9%), insomnia (31/534, 5.8%), and injection site pain (27/534, 5.1%).

Serious adverse event / deaths / other significant events

During the double-blind controlled maintenance phase, the incidence of deaths due to TEAEs was comparable in the aripiprazole IM depot 400 mg/300 mg group, oral aripiprazole tablets 10-30 mg group, and aripiprazole IM depot 50 mg/25 mg group. Three subjects died; one subject in the aripiprazole IM depot 400 mg/300 mg group (1/534, 0.2%) died due to pancreatic carcinoma, one subject (1/266, 0.4%) in the oral aripiprazole tablets 10-30 mg group died due to cardiac arrest, and one subject (1/131, 0.8%) in the aripiprazole IM depot 50 mg/25 mg group died due to a completed suicide No subjects treated with placebo died during the double-blind treatment phase. No TEAE leading to death was considered by the investigator to be related to trial treatment. Serious TEAEs were observed as follows: 26/534 (4.9%) in aripiprazole IM depot 400 mg/300 mg group, 15/266

(5.6%) in oral aripiprazole tablets 10-30 mg group, 11/131 (8.4%) in aripiprazole IM depot 50 mg/25 mg group, and 9/134 (6.7%) in placebo group. The only serious TEAEs reported for > 1% of aripiprazole IM depot 400 mg/300 mg subjects were schizophrenia and psychotic disorder and occurred as follows: 7/534 (1.3%) in aripiprazole IM depot 400 mg/300 mg group, 2/266 (0.8%) in oral aripiprazole tablets 10-30 mg group, 3/131 (2.3%)in aripiprazole IM depot 50 mg/25 mg group, and in 2/134 (1.5%) placebo group.

In all trials, 10 (0.6%) of 1539 aripiprazole IM depot 300-400 mg subjects and 1/168 (0.6%) aripiprazole IM depot < 300 mg subjects died due to TEAEs. Although the causes of death varied, approximately half of the deaths appeared to be cardiovascular-related (ie, myocardial infarction, cardiac arrest, cardio respiratory arrest, coronary artery insufficiency, arteriosclerosis). Treatment emergent AEs resulting in death were considered by the investigator to be either not likely related or unrelated to trial medication except for one event of cardiac arrest. One event of cardiac arrest was considered by the investigator to be possibly related to trial medication in the absence of other direct causes.

Laboratory findings

There were no clinically relevant mean changes in hematology, blood chemistry, and urinalysis. A higher incidence of potentially clinically relevant low WBC count in study 31-07-247, IM aripiprazole depot 400 mg/300mg: 6/260 (2.3%) versus oral aripiprazole 10-30 mg:2/258 (0.8%). No IM aripiprazole depot 50mg/25 mg had potentially clinically relevant low WBC value. During double blind maintenance phases, 3/534 (0.6%) aripiprazole IM depot 400 mg/300 mg subjects, 1/266 (0.4%) oral aripiprazole tablets 10-30 mg subjects, and 1/131 (0.8%) aripiprazole IM depot 50 mg/25 mg subjects had TEAEs related to WBC abnormalities. The abnormality in each group was neutropenia. Neutropenia was transient in 4 of the 5 subjects (including one subject with a medical history of neutropenia). Neutropenia continued in the fifth subject treated with aripiprazole IM depot 400 mg/300 mg); however, it was also present at screening in this subject and resolved during the open label study 31-08-248. No placebo subject had a TEAE related to WBC abnormalities. Neutropenia case typically started around day 16 after first injection, and lasts a median of 18 days.

Other safety findings

Weight changes

Changes are presented in Tables 10 and 11.

Table 10. Incidence of potentially clinically relevant weight gain and weight loss in study 31-07-247

Time Point Parameter	Aripiprazole IM Depot 400 mg/300 mg (N = 265)		Oral Aripiprazole 10-30 mg (N = 266)		Aripiprazole IM Depot 50 mg/25 mg (N = 131)	
	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]
At Last Visit						
Weight gain ≥ 7%[c]	264	25 (9.5)	266	31 (11.7)	131	6 (4.6)
Weight loss ≥ 7%[c]	264	27 (10.2)	266	12 (4.5)	131	13 (9.9)
Any Time During Phase						
Weight gain ≥ 7%[c]	264	42 (15.9)	266	43 (16.2)	131	8 (6.1)
Weight loss ≥ 7%[c]	264	40 (15.2)	266	27 (10.2)	131	18 (13.7)

Table 11. Incidence of potentially clinically relevant weight gain and weight loss in study 31-07-246

Time Point Parameter	Aripiprazole IM Depot 400 mg/300 mg (N = 269)		Placebo (N = 134)	
	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]
At Last Visit				
Weight gain ≥ 7%	267	17 (6.4)	134	7 (5.2)
Weight loss ≥ 7%	267	17 (6.4)	134	9 (6.7)
Any Time During Phase				
Weight gain ≥ 7%	267	27 (10.1)	134	10 (7.5)
Weight loss ≥ 7%	267	22 (8.2)	134	11 (8.2)

Abbreviations: CSR = clinical study report; IM = intramuscular.
a: Ne is the total number of subjects with a post-baseline weight result at the visit.
b: n is the number of subjects meeting the criteria for potential clinical relevance.
c: Change from Double-blind, Active-controlled Phase baseline.

The overall incidence of TEAEs related to weight was 14.3% (166/1160) for subjects treated with aripiprazole IM depot 300-400 mg ≥3 months and 18.6% (41/221) for subjects treated ≥24 months. There were increases in the incidence of the following weight-related TEAEs in subjects with longer exposure to aripiprazole IM depot 300-400 mg: increased weight (9.4% [109/1160] for ≥3 months exposure and 13.1% [29/221] for exposure ≥24 months) and decreased weight (5.0% [58/1160] for exposure ≥3 months to 5.9% [13/221] for exposure ≥24 months).

Extrapyramidal symptoms (EPS)

During double-blind maintenance phase treatment-emergent EPS and EPS-related AEs were reported for 98/534 (18.4%) aripiprazole IM depot 400 mg/300 mg subjects, 31/266 (11.7%) oral aripiprazole tablets 10-30 mg subjects, 16/131 (12.2%) aripiprazole IM depot 50 mg/25 mg subjects, and 13/134 (9.7%) placebo subjects. The difference between treatment groups in the incidence of treatment-emergent EPS and EPS-related AEs was considered clinically relevant and this is considered as a well known effect of atypical antipsychotics. In the aripiprazole IM depot 400 mg/300 mg group, the most frequently reported treatment-emergent EPS and EPS-related events were akathisia events (44/534 subjects, 8.2%) followed by parkinsonism events (37/534 subjects, 6.9%).

In all trials, 249/1539 (16.2%) aripiprazole IM depot 300-400 mg subjects had treatment-emergent EPS and EPS-related AEs. The overall incidence of treatment-emergent EPS and EPS-related AEs excluding akathisia was 10.7% (164/1539) of subjects treated with aripiprazole IM depot 300-400 mg. The overall incidence of treatment-emergent EPS and EPS-related AEs was 18.2% (211/1160) for subjects treated with aripiprazole IM depot 300-400 mg ≥ 3 months and 22.2% (49/221) for subjects treated ≥ 24 months. The overall incidence of EPS and EPS-related AEs excluding akathisia was 12.7% (147/1160) for aripiprazole IM depot 300-400 mg subjects treated ≥ 3 months and 19.0% (42/221) for subjects treated≥24 months.In study 31-08-248, the incidence of any treatment-emergent EPS or EPS-related AEs by time to onset after the first IM aripiprazole depot 400 mg/300 mg injection was ≤1.5% in patients without prior IM aripiprazole depot exposure.

Neuroleptic Malignant Syndrome (NMS)

In all trials, there was a single reported event of NMS among the IM aripiprazole depot treated population. The subject was randomized to and treated with aripiprazole IM depot 50 mg/25 mg in study 31-07-247. During the maintenance phase, on day 68, the subject was agitated with altered mental status. During hospitalization, NMS with dehydration, respiratory failure, metabolic acidosis, aspiration pneumonia, rhabdomyolysis, and acute renal failure was provisionally diagnosed. The investigator considered this case as serious, severe NMS in severity and potentially related to trial medication and led to trial discontinuation. This NMS case did resolve 20 days later with sequelae. (acute renal failure).

Suicidality

The incidence of suicidality-related TEAEs in the controlled trials was low overall, although it was noted that there were more suicide attempts and suicide ideation in IM depot aripiprazole treated patients than with oral aripiprazole treated patients . See Table 12.

Except for the fatal event of completed suicide in one subject in the aripiprazole IM depot 50 mg/25 mg group, all suicidality events resolved. In trial 31-07-246, 2 events of suicidal ideation were considered by the investigator to be at least possibly related to study drug. In trial 31-07-247, suicidal ideation in one aripiprazole IM depot 50 mg/25 mg subject was considered by the investigator to be definitely related to study drug, and all other TEAEs related to suicidal ideation/suicide were considered by the investigator to be unrelated or not likely related to study drug.

Table 12. Incidence of treatment emergent adverse events related to suicidal ideation/suicide in trials 31-07-246 and 31-07-247

Adverse Event (MedDRA Preferred Term)[a]	Aripiprazole IM Depot 400 mg/300 mg (N = 534) n (%)	Oral Aripiprazole 10-30 mg (N = 266) n (%)	Aripiprazole IM Depot 50 mg/25 mg (N = 131) n (%)	Placebo (N = 134) n (%)
Total	6 (1.1)	1 (0.4)	3 (2.3)	0 (0.0)
Completed suicide	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Suicidal ideation	4 (0.7)	0 (0.0)	2 (1.5)	0 (0.0)
Suicide attempt	2 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)

Abbreviations: AE = adverse event; IM = intramuscular; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

A TEAE is defined as an AE that started after start of study drug treatment; or if the event was continuous from baseline and was serious, study drug related, or resulted in death, discontinuation, interruption or reduction of study therapy.

Subjects with multiple AE terms within the same category are counted only once towards the category total.

Subjects with multiple AEs are counted only once towards the overall total of subjects with specified AEs.

[a] Adverse events terms related to suicidal ideation/suicide (MedDRA 13.1 primary terms): completed suicide, suicide of relative, suicide attempt, suicidal behaviour, suicide of companion, familial risk factor, suicidal ideation, depression suicidal, intentional self-injury.

Source: SCS CT-2.4.2.5.2.

Comparison on the time of onset of the suicidality related events did not reveal relevant difference between IM aripiprazole depot and oral aripiprazole.

Convulsions/Seizures

The incidence of convulsions/seizures was low in each treatment group. During double-blind maintenance phase, 1/131 (0.8%) aripiprazole IM depot 50 mg/25 mg subjects and 1/134 (0.7%) placebo subjects had TEAEs of convulsions/seizures.

In all trials, 2/1539 (0.1%) aripiprazole IM depot 300-400 mg subjects had TEAEs related to convulsions/seizures. Both events occurred in subjects treated with aripiprazole IM depot 300-400 mg ≤3 months (2/1160, 0.2%). One subject (1/168, 0.6%) treated with aripiprazole IM depot < 300 mg (any exposure) also had a convulsion. In study 31-08-248, convulsion occurred in 1/388 (0.3%) subjects ≤3 months after the first aripiprazole IM depot 400 mg/300 mg injection.

Orthostasis

The incidence of TEAEs related to orthostasis was low in subjects treated with aripiprazole IM depot 400 mg/300 mg. During double-blind maintenance treatment, these events were reported as follows: 2/534 (0.4%) in aripiprazole IM depot 400 mg/300 mg group, 2/266 (0.8%) in oral aripiprazole tablets 10-30 mg group, and 1/131 (0.8%) aripiprazole IM depot 50 mg/25 mg group and included postural dizziness in 1/266 (0.4%) in oral aripiprazole 10-30 mg group; syncope in 1/534 (0.2%) in aripiprazole IM depot 400 mg/300 mg group and 1/131 (0.8%) aripiprazole IM depot 50 mg/25 mg subjects; and orthostatic hypotension in 1/534 (0.2%) in aripiprazole IM depot 400 mg/300 mg group and 1/266 (0.4%) in oral aripiprazole 10-30 mg group. No placebo subject had TEAEs related to orthostasis. No subjects had vital signs indicative of orthostatic hypotension.In all trials, 16/1539 (1.0%) aripiprazole IM depot 300-400 mg subjects had TEAEs related to orthostasis. The overall incidence of TEAEs related to orthostasis in subjects treated with aripiprazole IM depot 300-400 mg was 1.2% (14/1160) for exposure ≥3 months and 1.4% (3/221) for subjects treated ≥24 months.

In study 31-08-248, TEAEs related to orthostasis that were reported during the trial included postural dizziness and syncope in patients without prior IM aripiprazole depot exposure. Postural dizziness and syncope were each reported for 1/314 (0.3%) subjects within 6-9 months after their first aripiprazole IM depot 400 mg/300 mg injection.

Local injection site reactions

During the double blind maintenance phase, injection site-related TEAEs in the aripiprazole IM depot 400 mg/300 mg group included injection site pain (28/534 subjects, 5.2%), injection site induration (8/534, 1.5%), injection site swelling (3/534, 0.6%), injection site erythema (3/534, 0.6%), and injection site discomfort, injection site pruritus, injection site reaction, and vessel puncture site pain (each in 1/534, 0.2%). Injection site reactions reported by oral aripiprazole 10-30 mg subjects included injection site pain (6/266, 2.3%), injection site erythema (3/266, 1.1%), and injection site induration and injection site swelling (each in 2/266, 0.8%). In the aripiprazole IM depot 50 mg/25 mg group, injection site-related TEAEs included injection site pain (1/131, 0.8%). In the aripiprazole placebo group, injection site-related TEAEs included injection site pain (5/134, 3.7%) and injection site erythema (1/134, 0.7%). In both efficacy studies, infrequent injection site reactions were observed; those seen were generally mild to moderate in severity, and resolved over time.

In all trials, 121/1539 (7.9%) aripiprazole IM depot 300-400 mg subjects had TEAEs related to the injection site. The overall incidence of TEAEs related to the injection site in subjects treated with aripiprazole IM depot 300-400 mg was 9.3% (108/1160) for subjects treated ≥3 months and 11.3% (25/221) for subjects treated ≥24 months. There were increases in the incidence of the following injection site-related TEAEs in subjects with longer exposure to aripiprazole IM depot 300-400 mg: injection site pain (95/1160 [8.2%] for subjects treated ≥3 months and 20/221 [9.0%] subjects treated for ≥24 months) and injection site induration (12/1160 [1.0%] and 6/221 [2.7%], respectively).

The incidence of TEAEs related to the injection site was low (< 1.0%) for each time period except for the injection site pain in subjects without prior exposure to aripiprazole IM depot. See Table 13.

Table 13 Incidence of TEAE related to injection site that started within a certain time period after first IM aripiprazole depot injection in trial 31-08-248

System Organ Class MedDRA Preferred Term	Aripiprazole IM Depot Treatment (Previous Aripiprazole IM Depot Exposure: None)				
	≤ 3 Months (N = 388) n (%)	3-6 Months (N = 350) n (%)	6-9 Months (N = 314) n (%)	9-12 Months (N = 264) n (%)	> 12 Months (N = 156) n (%)
Injection site erythema	3 (0.8)	2 (0.6)	2 (0.6)	1 (0.4)	0 (0.0)
Injection site induration	2 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site pain	21 (5.4)	4 (1.1)	4 (1.3)	3 (1.1)	0 (0.0)
Injection site swelling	2 (0.5)	3 (0.9)	0 (0.0)	1 (0.4)	0 (0.0)

Abbreviations: IM = intramuscular; MedDRA = Medical Dictionary for Regulatory Activities.Note: TEAE is defined as an AE that started after the start of trial medication treatment; or if the eventwas continuous from baseline and was serious, trial medication related, or resulted in death,discontinuation, or interruption or reduction of trial therapy. Subjects with multiple occurrences of TEAEs are counted only once per specific category.

Safety in special populations

Subgroup analyses by region, gender, age, sex, race, ethnicity, BMI did not reveal clinically meaningful differences in the safety profile of IM aripiprazole depot.

Pregnancies were reported in 7 subjects treated with aripiprazole IM depot (including one false positive test result) and 7 female partners of male subjects treated with aripiprazole IM depot.. Two additional pregnancies were reported during the double-blind treatment phase of ongoing trial 031-08-003. Three subjects (including one female partner) had normal full-term infants via spontaneous vaginal delivery with no complications and one infant was born with congenital bilateral club feet (considered unrelated to study drug); 3 subjects (all female partners) delivered full-term infants via cesarean section with no complications; one subject (female partner) delivered a healthy pre-term infant via vaginal delivery with no complications; 4 subjects (including one female partner) elected to terminate their pregnancy, and 2 subjects (including one female partner) had spontaneous abortions. In addition, an infant born to another female partner was referred to a neurologist at 7 months of age as the paediatrician was concerned that the infant may have cerebral palsy. No information has been received about this evaluation. This case was considered by investigator as unrelated to study drug. Based on the available data, IM aripiprazole depot should only be used during pregnancy after careful assessment of the benefit-risk profile in this population and considering the long-acting properties of the product.

IM aripiprazole depot has not been studied in the paediatric population and no safety data are available according to the waiver granted for all subsets of this population.

Safety related to drug-drug interactions and other interactions

No additional data other than the information derived from the clinical pharmacology of oral aripiprazole were presented. The CHMP noted that both efficacy studies (31-04-247 and 31-04-246) excluded patients treated with CYP3A4 inhibitors/inducers and CYP2D6 inhibitors (at all phases).

Discontinuation due to adverse events

During double-blind maintenance treatment, TEAEs resulting in drug discontinuation were as follows: 40/534 (7.5%) in aripiprazole IM depot 400 mg/300 mg group, 19/266 (7.1%) in oral aripiprazole group, 24/131 (18.3%) in aripiprazole IM depot 50 mg/25 mg group, and 18/134 (13.4%) in placebo group. Treatment-emergent AEs resulting in drug discontinuation reported for ≥ 1% of aripiprazole IM depot 400 mg/300 mg subjects were psychotic disorder and schizophrenia. TEAE related to EPS symptoms and leading to discontinuation were only reported in the aripiprazole IM depot 400mg/300mg group (n=8, 0.5%).

In all trials, one hundred forty-five (9.4%) of 1,539 aripiprazole IM depot 300-400 mg subjects had TEAEs resulting in drug discontinuation compared with 25/168 (14.9%) aripiprazole IM depot < 300 mg subjects. Most AEs in the IM depot <300 mg were due to treatment failure AEs (5.4% for each psychotic disorder and schizophrenia).

Post marketing experience

No post-marketing data for IM aripiprazole depot are presented since the product was not marketed in any countries at the time of the initial submission.

2.6.1. Discussion on clinical safety

The safety database for IM aripiprazole depot was considered adequate, considering that more than 1000 patients were treated for at least 6 months (patient exposure greater than 1600 subjects). No new safety concern was identified as compared to the safety profile of oral and rapid IM aripiprazole with the exception of local injection site reactions, and specifically injection site pain. Local injection site reactions were also reported as preclinical findings. A higher incidence of potentially clinically

relevant low WBC count was also observed in study 31-07-247 in the IM aripiprazole depot 400 mg/300mg arm (6/260, 2.3%) compared to the oral aripiprazole 10-30 mg arm (2/258 ,0.8%).The applicant clarified that among those patients having potentially clinically relevant low WBC, 3 out of 6 (50%) had low WBC values present at baseline in the IM aripiprazole depot 400/300 mg arm. However, from the CHMP viewpoint, the low WBC values persisted over time, hence the CHMP agreed with the PRAC recommendation to include this safety concern as important identified risk in the risk management plan. Additionally, the CHMP considered as relevant for the prescribers the time of onset of neutropenia. This is reflected in the SmPC accordingly.

The most frequently observed adverse drug reactions (ADRs) reported in ≥ 5 % of patients in two double-blind controlled clinical trials of Abilify Maintena were weight increased (9.0 %), akathisia (7.9 %), insomnia (5.8 %), and injection site pain (5.1 %).On the basis of the presented data regarding EPS (excluding akathisia) and weight gain, increasing incidences were observed over time.. Given the higher frequency of EPS symptoms with the IM aripiprazole depot 400/300 mg compared to oral aripiprazole 10-30 mg and increasing incidence over treatment duration , the PRAC and CHMP agreed for a post-authorization safety study (PASS) to further investigate this known safety concern with this specific formulation. The CHMP also noted that further data from the long term safety study 31-10-270 will be collected to monitor this safety concern.

Safety data on drug interactions are derived from the oral aripiprazole marketing authorisation. Both efficacy studies (31-04-247 and 31-04-246) excluded the concomitant use of CYP3A4 inhibitors/inducers and CYP2D6 at all phases. Given the pharmacokinetic findings (see 2.4.2), the CHMP agreed with the proposed dosing reduction in case of concomitant use of strong CYP3A4 inhibitors or strong CYP2D6 inhibitors and in poor CYP2D6 poor CYP2D6 metabolisers. In case of adverse reactions despite dose adjustments of Abilify Maintena, the necessity of concomitant use of CYP2D6 or CYP3A4 inhibitor should be reassessed.

The only serious TEAEs reported for > 1% of aripiprazole IM depot 400 mg/300 mg subjects were schizophrenia and psychotic disorder in both analysed datasets. These events were considered to be associated with the underlying psychotic disorder and no specific concerns were raised in this regard.

During the evaluation, the CHMP requested additional information on reports of inadvertent injection into a blood vessel, a possible risk with IM depot preparations. While no cases were reported in the clinical studies, the CHMP recommended to include a precautionary SmPC statement in section 4.9 to ensure close monitoring in such situation.

Overall, the CHMP considered that the safety profile of IM aripiprazole depot did not raise any new concern, with the exception of local injection site reactions and this is reflected accordingly in the SmPC. The proposed legal status is “medicinal product subject to medical prescription” and no further restrictions were recommended by the CHMP.

2.6.2. Conclusions on the clinical safety

Based on the data collected to date, the safety profile of IM aripiprazole depot appeared favourable and similar to that of oral aripiprazole. From the safety database, all the adverse reactions reported in clinical trials and postmarketing (for oral aripiprazole only) have been included in the SmPC.

As detailed in the risk management plan, the CHMP considers and agreed to the pharmacovigilance plans as described below in section 2.8. :

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 8.2 the PRAC considers by consensus decision that the risk management system for Aripiprazole (Abilify Maintena) in the maintenance treatment of schizophrenia in adults, could be acceptable provided an updated risk management plan is submitted with the following changes:

- Leukopenia is considered to be an important identified risk based on clinical data, where the incidence of IM depot related leukopenia was almost 3 times higher than what was observed in the oral route (2.3% vs. 0.8%). There seems to be a different risk incidence related to this particular formulation. Leukopenia should be included as important identified risk.

- a finalised protocol of "Extrapyramidal symptoms in patients treated with Abilify Maintena: Cohort study with a 2-year follow-up using European longitudinal electronic medical records or claims databases" should be submitted within 2 months.

The CHMP endorsed this advice without changes.

The applicant amended the RMP accordingly and the revised RMP was agreed by the CHMP.

Safety concerns

Summary of safety concerns	
Important identified risks	Extrapyramidal syndrome, including tardive dyskinesia
	NMS
	Leukopenia
Important potential risks	Seizure
	Hyperglycemia/diabetes
	Suicide-related events
	Orthostatic hypotension
	Dyslipidemia
Missing information	Use in pregnancy and lactation
	Use in elderly patients above 65 years of age

Pharmacovigilance plans

Description	Due date

An open-label, multi-center, rollover, long-term study of aripiprazole intramuscular depot in patients with schizophrenia (Study Protocol No. 31-10-270)	Results of the analysis of EPS related events to be presented in the RMP: September 2014 Final clinical study report: 2019
Post-authorization safety study (PASS) related to Extrapyramidal symptoms in patients treated with Abilify Maintena: Cohort study with a 2- year follow-up using European longitudinal electronic medical records or claims databases: - Germany (Statutory Health Insurances [SHI] claim database; Spain (Sistema d' Informació per al Desenvolupament de la Investigació en Tencio Primària [SIDIAP]); Sweden (National Presciption Register and National PatientRegister.	Anticipated Launch Dates: Germany Q2/2014, Spain: Q3/2014, Sweden: Q1/2014 Date of first feasibility analysis: Germany: Q2/2016, Spain: Q3/2016, Sweden: Q1/2016 Expected date for targeted sample size: Germany: Q2/2017, Spain: Q3/2017, Sweden: Q1/2017 Expected date of study report: Germany: Q4/2019, Spain: Q1/2020, Sweden: Q3/2019

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
EPS including Tardive Dyskinesia	**SmPC:** **Section 4.4: Special warnings and precautions for use** "Tardive dyskinesia. In clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY MAINTENA, dose reduction or discontinuation should be considered (see section 4.8). These symptoms can temporally deteriorate or can even arise after discontinuation of treatment." **Section 4.8 Undesirable effects** "Nervous system disorders: Common: Extrapyramidal disorder, akathisia, tremor, dyskinesia. Uncommon: Dystonia, tardive dyskinesia, Parkinsonism, movement disorder, psychomotor hyperactivity, Cogwheel rigidity" "In the pivotal trials in stable patients with schizophrenia, ABILIFY MAINTENA was associated with a higher frequency of EPS symptoms (18.4 %) than oral aripiprazole treatment (11.7 %). Akathisia was the most frequently observed symptom (8.2 %) and typically starts around day 10 after first injection, and lasts a median of 56 days. Subjects with akathisia typically received anti-cholinergic medicines as treatment, primarily benzatropine mesilate and trihexyphenidyl. Less often substances such as propanol and benzodiazepines (clonazepam and	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	diazepam) were administered to control akathisia. Parkinsonism events followed in frequency (6.9 % ABILIFY MAINTENA, 4.15 % oral aripiprazole 10-30 mg tablets group and 3.0 % placebo, respectively)." "Dystonia Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.	
Leukopenia	**SmPC:** **Section 4.8 Undesirable effects** "Blood and lymphatic system disorders- uncommon: white blood cell count decreased, neutropenia, neutrophil count decreased, not known frequency: leukopenia" *Leukopenia* Neutropenia has been reported in the clinical program with ABILIFY MAINTENA and typically starts around day 16 after first injection, and lasts a median of 18 days.	
NMS	**SmPC:** **Section 4.4: Special warnings and precautions for use** "Neuroleptic Malignant Syndrome NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase,myoglobinuria (rhabdomyolysis), and acute renal failure. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including aripiprazole, must be discontinued (see section 4.8)." **Section 4.8 Undesirable effects** "Nervous system disorders – not known frequency: NMS"	None
Seizure	**SmPC:** **Section 4.4: Special warnings and precautions for use** Seizure: In clinical trials, uncommon cases of seizure	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures (see section 4.8)." **Section 4.8 Undesirable effects** "Nervous system disorders – not known frequency: Grand Mal Convulsion"	
Hyperglycemia/ diabetes	**SmPC:** **Section 4.4: Special warnings and precautions for use** "Hyperglycaemia and diabetes mellitus: Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotic agents, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY MAINTENA, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control (see section 4.8)." **Section 4.8 Undesirable effects** "Metabolism and nutrition disorders- common: diabetes, uncommon: hyperglycaemia"	None
Suicide	**SmPC:** **Section 4.4 Special warnings and precautions for use** "The occurrence of suicidal behavior is inherent in psychotic illnesses, and in some cases has been reported early after initiation or switch of antipsychotic treatment, including treatment with aripiprazole (see section 4.8). Close supervision of high risk patients should accompany antipsychotic treatment. **Section 4.8 Undesirable effects** "Nervous system disorders – uncommon: suicidal ideation, not known frequency: completed suicide, suicide attempt"	None
Orthostatic hypotension	**SmPC:** **Section 4.8 Undesirable effects** "Vascular disorders- Uncommon: orthostatic hypotension. Not known: Syncope"	None
Dyslipidemia	**SmPC:** **Section 4.8 Undesirable effects** "Metabolism and nutrition disorders- uncommon: hypercholesterolaemia, hyperinsulinaemia, hyperlipidaemia, hypertriglyceridaemia; Investigations:	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	blood cholesterol decreased, blood triglycerides decreased	

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Oral aripiprazole has been on the market for several years in the treatment of schizophrenia in adults, and has a well characterised efficacy and safety profile. The present application relates to the depot preparation of aripiprazole intended to be used as a possible maintenance treatment option for adult patients with schizophrenia and suggested to improve treatment adherence and compliance with a proposed monthly administration instead of daily oral intake. Such treatment option may be considered as an important medical need given its potential association with improved long term outcomes for patients with schizophrenia.

In an adequately designed pivotal study 31-07-247, non-inferiority of aripiprazole IM depot 400 mg/300 mg to oral aripiprazole tablets 10-30 mg was demonstrated and the assay sensitivity was confirmed. The primary efficacy endpoint was the proportion of subjects experiencing impending relapse. The estimated relapse rate by end of Week 26 was 7.12% in the aripiprazole IM depot 400 mg/300 mg group and 7.76% in the oral aripiprazole tablets 10-30 mg group, a difference of −0.6%. The 95% CI (−5.26, 3.99) for the difference in the estimated proportion of subjects experiencing impending relapse by end of Week 26 excluded the predefined non-inferiority margin of 11.5%.

The secondary efficacy endpoint, time to impending relapse, was similar in the aripiprazole IM depot 400 mg/300 mg group and the oral aripiprazole tablets 10-30 mg group (log-rank test, p = 0.9920). The risk of impending relapse was similar in the aripiprazole IM depot 400 mg/300 mg group as compared with the oral aripiprazole tablets 10-30 mg group (hazard ratio = 0.991, 95% CI = 0.545, 1.803). The time to impending relapse was also statistically significantly delayed (ie, improved) in the aripiprazole IM depot 400 mg/300 mg group compared with the aripiprazole IM depot 50 mg/25 mg group (log-rank test, p < 0.0001). Other secondary results were also consistent with the primary efficacy analysis showing stabilisation of the psychotic symptoms in patients treated with IM aripiprazole depot 400mg/300 mg and suggested that lower dose was not efficacious in the proposed indication. Moreover, the proportion of responders was statistically significantly higher in the aripiprazole IM depot 400 mg/300 mg group than in the aripiprazole IM depot 50 mg/25 mg group (p = 0.0001).

In the supportive study 31-07-246, the primary efficacy variable was the time to impending relapse in adult subjects with schizophrenia who maintained stability for at least 12 consecutive weeks on aripiprazole IM depot 400 mg/300 mg. Results showed that time to impending relapse was significantly shorter for subjects randomized to placebo compared with subjects randomized to aripiprazole IM

depot 400 mg/300 mg in the double blind maintenance phase (p < 0.0001; log-rank test) further supporting the primary efficacy analysis.

Uncertainty in the knowledge about the beneficial effects

Both studies (31-07-247 and 31-07-246) included patients stabilised with oral aripiprazole, for at least 8 weeks in study 31-07-247 and up to 12 weeks in study 31-07-246. Whilst overall, the CHMP considered that the patients included in the pivotal study 31-04-247 was sufficiently representative of the intended population, it is noted that no efficacy data are available for patients stabilised with oral aripiprazole for shorter time periods.

Uncertainties in the dosing recommendation for CYP2D6 known poor metabolisers or concomitant users of CYP3A4 inhibitors/inducers and CYP2D6 inhibitors subject to higher exposure were identified and have been adequately addressed in the SmPC.

Risks

Unfavourable effects

No new safety issues have been identified in preclinical studies conducted with IM aripiprazole depot as compared to oral aripiprazole, with the exception of local injection site reactions. Local injection site reactions were confirmed in clinical trials, in particular injection site pain

Furthermore, the incidence of leukopenia-related events (low WBC) was almost 3 times higher than what was observed in the oral route (2.3% vs. 0.8%) in the pivotal study. There seems to be a different risk incidence related to this particular formulation. Therefore, leukopenia is considered as an important identified risk in addition to the other important identified/potential risks already existing for the oral aripiprazole (EPS and tardive dyskinesia, NMS; seizures, hyperglycemia/diabetes, suicide-related event, orthostatic hypotension and dyslipidemia).

Uncertainty in the knowledge about the unfavourable effects

Data are expected to be collected via a post-authorization safety study (PASS) to further investigate EPS given the higher frequency of EPS symptoms observed with the IM aripiprazole depot 400/300 mg as compared to the oral route, and increasing incidence over treatment duration. In addition, the long term open label safety study 31-10-270 is ongoing and should generate additional data with respect to this observation.

Elderly population was not studied. This is considered as missing information in the Risk Management Plan.

Pregnancies were reported during the clinical studies. Based on preclinical findings and limited clinical data, IM aripiprazole depot profile in this population is considered not fully characterised and the product should only be used during pregnancy after careful assessment of the benefit-risk profile in this population and considering the long-acting properties of the product. Use in pregnancy is considered as missing information in the Risk Management Plan.

Benefit-risk balance

Importance of favourable and unfavourable effects

The non inferiority of IM aripiprazole depot versus oral aripiprazole was demonstrated in the proposed dosing regimen in patients orally stabilized with aripiprazole for a sufficient long term period (at least 8 weeks). The only new safety issues as compared to oral aripiprazole of importance were the injection pain. Although these might affect the adherence to treatment, they were considered to be manageable with routine pharmacovigilance.

Benefit-risk balance

Having considered the benefits of this new depot formulation (aripiprazole) over the limited new risks identified as compared to the oral aripiprazole, already approved in the treatment of schizophrenia, the CHMP concluded that the benefit-risk balance for Abilify Maintena is positive with the following indication:

"Abilify Maintena is indicated for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole."

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Abilify Maintena in the "maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole" is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.