SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Abilify. For information on changes after approval please refer to module 8.

1. Introduction

Schizophrenia is a major psychotic disorder. Its essential features consist of a mixture of characteristic signs and symptoms that have been present for a significant length of time during a 1-month period (or for a shorter time if successfully treated), with some signs of the disorder persisting for at least 6 months.

The characteristic symptoms of schizophrenia have often been conceptualized as falling into two broad categories positive and negative (or deficit) symptoms with a third category, disorganized, recently added because statistical analyses have revealed that it is a dimension independent of the positive symptom category, where it was previously included. The positive symptoms include delusions and hallucinations. Disorganized symptoms include disorganized speech (thought disorder) and disorganized behaviour and poor attention. Negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, and decreased initiation of goal-directed behaviour (avolition).

The onset of schizophrenia typically occurs during adolescence or early adulthood. It affects men and women with equal frequency. The peak age at onset for males, however, is the early 20s, and for women it is the late 20s and early 30s. The majority of patients alternate between acute psychotic episodes and stable phases with full or partial remission. Inter-episode residual symptoms are common. This often-chronic illness can be characterized by three phases that merge into one another without absolute, clear boundaries between them. These phases, which form the structure for integrating treatment approaches, are described below:

Acute phase. During this florid psychotic phase, patients exhibit severe psychotic symptoms, such as delusions and/or hallucinations and severely disorganized thinking, and are usually unable to care for themselves appropriately. Negative symptoms often become more severe as well.

Stabilization phase. During this phase, acute psychotic symptoms decrease in severity. This phase may last for 6 or more months after the onset of an acute episode.

Stable phase. Symptoms are relatively stable and, if present at all, are almost always less severe than in the acute phase. Patients can be asymptomatic; others may manifest non-psychotic symptoms, such as tension, anxiety, depression, or insomnia. When negative (deficit) symptoms and/or positive symptoms, such as delusions, hallucinations, or thought disorder, persist, they are often present in attenuated, non-psychotic forms (e.g., circumstantiality rather than looseness, illusions rather than hallucinations, overvalued ideas rather than delusions).

There are a number of antipsychotics in use but none is ideal in particular because their safety profile is complex. The *in vitro* affinity profile of aripiprazole for dopamine and serotonin receptors is similar to the one of so-called atypical antipsychotics. It is postulated that aripiprazole's mechanism of action is novel as it involves a combination of partial agonist action (agonist/antagonism) at dopamine D2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors.

2. Chemical, pharmaceutical and biological aspects

Composition

Abilify contains aripiprazole as the active ingredient. It is presented in the form of 5, 10, 15, and 30 mg tablets.

Other ingredients include lactose monohydrate, starch (maize), microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate (vegetable origin), purified water and colour (Iron oxide red).

Abilify tablets are packaged in aluminium perforated unit dose blisters in a carton.

Active substance

Manufacture

Information on aripiprazole has been supplied in the form of an active substance master file ('EDMF').

Aripiprazole is a quinolinone derivative with the chemical name 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]- 3,4-dihydro-2(1H)-quinolinone.

The active substance does not contain any chiral centres and does not exhibit any optical isomerism.

Aripiprazole active substance is a white crystalline powder and is practically insoluble in water and its solubility is pH dependent. Therefore, a particle size effect on dissolution of the tablets can be expected. In order to ensure batch-to-batch consistency of the product, and to ensure adequate bioavailability, aripiprazole is subject to milling.

Aripiprazole can exist in several crystalline forms, Form Iwas chosen for the development and commercialisation..

Aripiprazole is synthesised by a 2-step process. In the first step, 7-hydroxy-3,4-dihydro-2(H)-quinolinone is transformed into an intermediate, which is reacted with 1-(2,3-dichlorophenyl) piperazine hydrochloride to obtain aripiprazole. The process, specifications and control methods are adequately described in the restricted section of the EDMF.

Specification

The active substance specification includes tests for description, identity (IR, HPLC, and Power X ray diffraction), assay (HPLC), related impurities (HPLC), heavy metals, particle size, etc.

The analytical methods used in routine controls are suitably described. Impurity limits in the specification are justified by toxicology studies.

Batch data are provided for 54 production batches produced in the manufacturing site, the industrial process manufactured 17 of these batches.

The tests and limits in the specification are appropriate for controlling the quality of Aripiprazole.

Stability

Stability studies under long term ICH conditions (25°C/60%RH and 40°C/75%) up to 12 months in three production-scale batches and under stress conditions (60°C, 25°C/91%RH, 40°C/75%RH) up to 6 months in 1 production batch up to 6 months have been performed. The stability batches were stored in a polyethylene bag / aluminium foil-polyethylene laminated bag or in open dishes. Methods are validated and stability indicating. The parameters tested are appearance, particle size, loss on drying, identification and drug related impurities / degradation products. These data provided are sufficient to confirm the proposed re-test period.

Other ingredients

All excipients used are described in the European Pharmacopoeia. Magnesium stearate is of vegetable origin. Colours meet the general requirements as described in EC Directive 95/45/EC.

The only ingredient from animal origin is lactose monohydrate using milk and calf rennet of bovine origin during its preparation. The manufacturer has provided confirmation that the milk is sourced from healthy animals in the same conditions as milk collected for human consumption and that the calf rennet complies with the public statement EMEA/CPMP/571/02.

Aripiprazole tablets are packaged in aluminium perforated unit dose blisters. The specifications and testing standards for the primary packaging components used are presented and are acceptable

Product development and finished product

Abilify 5 mg, 10 mg, 15 mg and 30 mg strength tablets formulation of the active substance aripiprazole were selected as the proposed commercial strengths. However, extensive information on 2 mg and 20 mg strength aripiprazole tablets have been provided as supportive information.

The product development has taken into consideration the physicochemical characteristics of the active drug substance such as poor aqueous solubility, hygroscopic properties, stability, particle size, polymorphism, and biopharmaceutical issues such as dissolution rate.

The formulation contains stable, milled crystalline aripiprazole because of the limited solubility in water and the hydrophobic nature of the active substance. Fluid bed wet granulation process was developed as the manufacturing process for the tablets. The excipients included in the formulation were chosen and adjusted in order to achieve a dosage form with an accurate therapeutic onset.

The formulation shows a good bioavailability and the results of pharmacokinetic and in vitro studies support the bioequivalence between clinical and commercial tablets.

The finished product is manufactured in 9 steps: weighing, preparation of binding solution, granulation and drying, sizing, dispersion and blending of colour, lubrication, compression, control and packaging.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process in four industrial batches.

Product Specification

The product specifications include tests by validated methods for appearance, identification (HPLC and IR), assay (HPLC), impurities / degradation products (HPLC), uniformity of contents, dissolution and microbial purity.

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

A total of 28-batch analyses covering all strengths of Aripiprazole tablets are presented, and the results confirm satisfactory uniformity of the product at release.

Stability of the Product

Three batches of each strength of tablets manufactured at commercial scale, were placed on stability according to ICH Guideline, each batch was packaged in aluminium/aluminium blisters.

Photostability studies (loose tablets using one lot of each strength over a period of 600 hours), open dishes studies at high humidity (loose tablets using one lot of each strength over periods of 12 months at 25ºC/60%RH and 3 months at 40ºC/75%RH) and cycling stress studies (aripiprazole tablets packaged in blisters stored for 10 hours at –15ºC and 10 hours at 30ºC, with a complete cycle every 24 hours for 14 days) were carried out on aripiprazole tablets.

Also, samples of all strengths packaged in aluminium blisters were evaluated at 50ºC.

Results have been generated by validated, stability indicating methods and show satisfactory stability. These results support the shelf life and storage conditions stated in the SPC.

Bioavailability and Bioequivalence.

Since the solubility of the active substance is pH dependent and highly permeable, differences in formulation and/or method of manufacture may affect the bioavailability to a considerable extent. Therefore, three effects related to formulation development have been investigated: (1) equivalence between anhydrous and hydrated forms of the active substance, (2) dose normalised bioequivalence between strengths, and (3) equivalence between development and market products. In addition the relative bioavailability of capsule and tablet versus ethanolic solution has been determined and a food/drug interaction study has been performed as well. In general, the studies comply with the current requirements and demonstrated that the formulation shows reasonably good bioavailability and the results of pharmacokinetic and in vitro studies support the bioequivalence between clinical and commercial tablets and that no special recommendations with respect to food intake are necessary.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Abilify is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The aripiprazole tablets intended for marketing are well suited; the manufacturing process is under control and ensures both batch to batch reproducibility and compliance with standard procedures and specifications; the analytical methods have been validated and seem to be suitable to ensure consistent quality of the active substance and the finished product, the synthetic pathway is presented and the structure and impurity profile are well characterised and in line with current ICH guidelines. The stability data on the active substance supports the proposed re-testing period.

The stability data of the finished product in the proposed packages support the shelf life stated in the SPC.

At the time of the CPMP opinion there were some unresolved minor quality issues which had no impact on the benefit/risk profile. The applicant committed in a letter of undertaking to provide the necessary information as follow up measures within an agreed timeframe.

3. Toxico-pharmacological aspects

Introduction

Aripiprazole is a new antipsychotic belonging to the class of atypical antipsychotic drugs. It has been proposed that aripiprazole antipsychotic action could be mediated through a combination of partial agonist action at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors

Pharmacology

- **Primary pharmacodynamics (in vitro/in vivo)**

In vitro 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 acts as a D_2 receptor partial agonist *in vitro*: (1) 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 (2) in cultured rat anterior pituitary cells, aripiprazole 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-$HT_{2A\text{-antagonist}}$ activity. Aripiprazole demonstrates agonist activity at (presynaptic) dopamine auto-receptors. Thus, aripiprazole: (1) 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; (2) 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.

In vivo studies

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 (Acc) neurons, activated monosynaptically by stimulation of the parafascicular nucleus of the thalamus (Pf), 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} antagonists WAY-100635. Additionally, in acutely dissociated hippocampal pyramidal neurons of the rat, aripiprazole (at 10^{-5}M) significantly reduce 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 pharmacodynamics and Safety pharmacology**

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 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 D_2 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 D_2 receptor blockade (haloperidol, chlorpromazine, risperidone) act in an additive manner to block DA-mediated behaviour 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 D_2 receptor antagonists enhanced blockade of pituitary D_2 receptors culminating in increased prolactin levels.

Pharmacokinetics

A number of *in vitro* and *in vivo* studies were carried out to investigate the metabolism and pharmacokinetics of aripiprazole employing species routinely used for toxicologic assessment (i.e., mouse, rat, rabbit, dog, and monkey) after single or multiple dose by oral and parenteral administration.

Sensitive and specific high performance liquid chromatography (HPLC/UV), gas chromatography coupled with mass spectrometry (GC/MS), and/or liquid chromatography with tandem mass spectrometry (LC/MS/MS) methods were developed and validated for determination of concentrations of aripiprazole and/or its metabolites in plasma, bile, urine, and/or brain of mice, rats, rabbits, dogs, and monkeys

- **Absorption- Bioavailability-Distribution**

The pharmacokinetics of aripiprazole were 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.

Placenta and milk transfer

Following [^{14}C]-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 [^{14}C]-aripiprazole to lactating rats. In addition, the milk vs. blood concentration ratios was 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 SPC.

- **Metabolism (in vitro/in vivo)- Excretion**

After an intravenous single dose, the terminal phase elimination half-life of aripiprazole in plasma was about 3 h in mice, 1 h in rats, 2-5 h in dogs, and 4 h in monkeys. In comparison, the terminal phase elimination half-life after intravenous administration in humans averaged 99 h (range 44 to 168 h). The systemic clearance (CLT) in mice, rats, dogs, monkeys, and humans was 19-24, 83-110, 21-29, 14, and 0.72 mL/min/kg, respectively. In humans, the long terminal phase elimination half-life and low CLT suggest much slower rate of elimination of aripiprazole as compared to animals.

In rats, monkeys, and humans, aripiprazole was primarily metabolized by three biotransformation pathways which were qualitatively similar across species: dehydrogenation to form OPC-14857, the major circulating metabolite in human, hydroxylation to form DM-1451, and N-dealkylation; to form OPC-3373 and N-2,3-dichlorophenylpiperazine (DCPP). Aripiprazole is primarily metabolized by CYP3A4 and CYP2D6 isozymes. Aripiprazole was mainly eliminated via metabolic clearance and

metabolites of aripiprazole were eliminated by both renal and biliary routes in monkeys and humans and predominantly by biliary route in rats.

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*, indicating that the presence of metabolites in the plasma did not affect the protein binding of aripiprazole. Therefore, significant drug interactions due to the protein binding displacement are unlikely.

Drug interactions

In rats, the potential of aripiprazole to induce hepatic drug-metabolizing enzymes was investigated and did not show induction of CYP enzymes.

The potential for inhibitory activity (IC_{50}) of aripiprazole and its active metabolite, OPC-14857, on CYP1A2, -2C9, -2C19, -2D6, and -3A4 was investigated in several *in vitro* systems using human cytochrome P450 enzymes. These *in vitro* data suggest that aripiprazole and its metabolite OPC-14857 did not significantly inhibit the above enzymes at clinically relevant concentrations.

Clinical drug-drug interactions are further discussed in the clinical part.

Toxicology

The safety of aripiprazole has been evaluated in single- and repeat-dose oral toxicity studies in rats and monkeys, a battery of *in vitro* and *in vivo* genetic toxicity studies, carcinogenicity studies in mice and rats, reproductive and developmental toxicity studies in rats and rabbits, local tolerance studies in rabbits, antigenicity studies in guinea pigs, studies of serum hormone levels in mice and rats, and physical dependence and abuse potential studies in rats and monkeys. Dose range-finding studies were conducted in the appropriate species to assist in dose selection for definitive repeat-dose toxicity, oral micronucleus, reproductive toxicity, and carcinogenicity studies. Additionally, the toxicity of two metabolites of aripiprazole in animals and humans (OPC-14857, OPC-3373) was evaluated in single-dose studies in rats, and the metabolite DCPP was evaluated in a bacterial gene-mutation test. Aripiprazole was administered as a suspension in 5% gum arabic solution in all oral toxicity studies. All definitive nonclinical toxicology studies and the majority of dose range-finding and investigative studies were conducted in compliance with Good Laboratory Practice regulations.

- **Single dose toxicity**

In rats, the median lethal dose after oral administration of aripiprazole was approximately in the range of 950-700 mg/kg. Drug-related clinical findings preceding death included principally: decreased spontaneous motor activity, convulsions, ataxia, tremors, and catalepsy. After intravenous administration, no death and no clinical findings were noted up to the highest feasible dose of 2 mg/kg.

In monkeys, the median lethal dose after oral administration of aripiprazole was greater than 2000 mg/kg. Severe drug-related clinical effects were noted primarily during week 1 and included: impaired motor activity, hyporeactivity to external stimuli, catalepsy, tremors and prone and/or lateral position. All clinical signs were considered pharmacologically mediated and resolved on or before day 11 with the exception of tremors and impaired motor activity in one high-dose female that persisted through the end of the study. No gross pathologic changes were observed in the 2000 mg/kg animals necropsied. After intravenous administration, there were no aripiprazole-related findings at any dose up to the highest feasible dose of 1 mg/kg.

- **Repeat dose toxicity (with toxicokinetics)**

The main oral studies in rats and monkeys are listed chronologically in the following tables:

Main Repeat-dose oral studies in rats with TK

Duration (weeks)	Dose levels mg/kg/day	NOAEL mg/kg/day	AUC $_{0\text{-}24h}$(ng.h/ml) ratio to humans**	
			NOAEL (M/F)	High Dose (M/F)
13*	0, 2, 6, 20	6 (M), 2 (F)	nd	0.2/0.5
52	0, 1, 3, 10	3 (M), 1 (F)	<0.1	<0.1
4*	0, 60, 100	Not determined	N/A	9.5/12.6
26*	0, 10, 30, 60	Not determined	N/A	14/9.5

*recovery period; nd: no data. ** Human AUC $_{0\text{-}24h}$= 7591 ng.h/ml at 30 mg/day

Main Repeat-dose oral studies in monkeys with TK

Duration (weeks)	Dose levels mg/kg/day	NOAEL mg/kg/day	AUC $_{0\text{-}24h}$(ng.h/ml) ratio to humans**	
			NOAEL (M/F)	High Dose (M/F)
13*	0, 0.5, 1, 5, 25	1	nd	0.5/0.6
52	0, 0.5, 5, 25	0.5	<0.1	1.4/0.8
39	0, 25, 50, 75/100	Not determined	N/A	2.7/3.1

* recovery period; nd: no data. ** Human AUC $_{0\text{-}24h}$= 7591 ng.h/ml at 30 mg/day

Aripiprazole did not cause any life-threatening toxicity when administered to rats at doses up to 60 mg/kg/day for 6 months or to monkeys at doses up to 75 mg/kg/day for 9 months. Dose-limiting CNS-related clinical signs and the majority of morphologic tissue changes were considered to be a consequence of exaggerated pharmacology or drug-related perturbations of serum prolactin levels.

In rats, the main changes included dose-related pulmonary histiocytosis, adrenocortical hypertrophy and increased adrenal and ovarian lipofuscin pigments, and associated adrenocortical cell loss after chronic treatment at high doses.
In monkeys, gallsand and gallstones and minimal focal hepatolithiasis were observed at high doses as a consequence of concentration and precipitation of sulfate conjugates of hydroxy metabolites of aripiprazole in the terminal biliary tree and gallbladder. No other target organs of toxicity were identified in the monkey.

- **Genotoxicity in vitro and in vivo (with toxicokinetics)**

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 (with toxicokinetics)**

The carcinogenic potential of aripiprazole was evaluated in two 104-week dietary carcinogenicity studies in mice, one 104-week dietary carcinogenicity study in F344 rats, and one 104-week oral carcinogenicity study in SD rats.

Design and TK of carcinogenicity studies in mice and rats

Route of admin.	Strain	Dose levels mg/kg/day	AUC $_{0\text{-}24h}$(ng.h/ml) ratio to humans*	
			Male	Female
Diet	ICR mice	1	0.1	<0.1
		3	0.1	0.1
		10	0.5	0.3
Diet	ICR mice	30	1.4	0.9
Diet	F344 rats	1	-	-
		3	<0.1	<0.1
		10	<0.1	0.1
Oral	SD rats	10	0.3	1.2
		20	2.7	3.4
		40	7.3	10.1
		60	11.8	13.5

* Human AUC $_{0\text{-}24h}$= 7591 ng.h/ml at 30 mg/day

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. 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 females. Increases in mammary and pituitary neoplasms as well as other drug-related mammary/reproductive tissue alterations in females were considered to be secondary to aripiprazole-related increases in serum prolactin.

In the rat, 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 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.

SD Rat oral carcinogenicity. Main neoplastic findings

Dose (mg/kg/day)		0		10		20		40		60	
Gender		M	F	M	F	M	F	M	F	M	F
Total evaluated		109	110	55	55	55	55	55	55	55	55
Nb of animals with neoplastic findings											
Adrenal cortex	Adenoma	5	5	2	1	1	3	3	4	2	6
	Carcinoma	2	0	0	0	0	0	0	2	2	6
	Tumors combined	7	5	2	1	1	3	3	4	4	12

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 ($AUC_{0\text{-}24}$ h) that were equivalent (mice) and up to approximately 14 times greater than (rats) exposure at the maximum recommended dose in humans (30 mg). The maximum non-carcinogenic dietary doses of 1 mg/kg/day (mice) and 3 mg/kg/day (rats) resulted in subtherapeutic exposures (x25 and x300 lower), whereas 12- and 10-fold multiples of exposure was achieved at the maximum non-carcinogenic dose (60 and 40 mg/kg) in male and female rats, respectively, in the oral carcinogenicity study.

The applicant conducted a 70-week investigative study in rats in order to address the pathogenesis of the adrenocortical changes and female specific tumorigenic findings.

The main proposed mechanism is related to cytotoxicity due to increased oxidative stress induced by aripiprazole, rather than increased adrenocortical hormone production, as this has been considered as minor in the treatment period.. Although not fully proven, it is considered that the approach to understand the risk posed into humans by these tumorigenic properties of aripiprazole has been appropriately addressed. However, as the relevance for humans posed by this effect remains incompletely clarified, a specific post-marketing follow-up measures have been requested by the CPMP. This is reflected in the SPC section 5.3.

- **Reproductive and developmental studies**

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

abnormalies 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 F_1 fetuses and pups, and minimally decreased reproductive performance (fertility index) of F_1 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 F_1 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. This is reflected in the SPC section 5.3.

- **Local tolerance**

Aripiprazole was non-irritating to rabbit skin and was considered non-irritating to the rabbit eye using the Draize numerical evaluation method.

- **Other toxicity studies**

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.

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.

Environmental risk assessment:

The assessment is based on the physical/chemical properties of aripiprazole, particularly the relatively low partition coefficient that suggests that it is not likely to accumulate in the environment, and on the human metabolic data, which indicates that much of the drug is metabolised to relatively inactive metabolites. The risk of an adverse environmental impact from use of aripiprazole in Europe is not considered to be of concern.

Discussion on the non-clinical aspects

Aripiprazole is a new antipsychotic belonging to the class of atypical antipsychotic drugs. It has been proposed that aripiprazole antipsychotic action could be mediated through a combination of partial agonist at dopamine D2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors. The non-clinical characterization of aripiprazole as a dopamine D2 receptor partial agonist at pituitary lactotrophs predicts a low potential to induce hyperprolactinemia in humans but it may be dose related. Studies on the sedative liability of aripiprazole suggest a reduced sedative potential compared to typical antipsychotics. The safety pharmacology profile of aripiprazole reveals that this agent exhibits a reduced impact on cardiovascular, renal and gastrointestinal systems.

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.

Studies in rats suggest that there is a potential for foetal and neonatal exposure to aripiprazole if administered to pregnant or lactating women. This information is included in section 4.6 of the SPC.

Aripiprazole is primarily metabolized by CYP3A4 and CYP2D6 isozymes. Aripiprazole was mainly eliminated via metabolic clearance and metabolites of aripiprazole were eliminated by both renal and biliary routes in monkeys and humans and predominantly by biliary route in rats.

The gallbladder stone formation observed in monkeys appears to be species specific. The risk of gallstone formation in patients is probably very low since sulfate conjugated metabolites of aripiprazole do not reach sufficient biliary concentrations in humans and since no indication of such a risks occurred during the clinical trials. This is described in the SPC (section 5.3).

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 is 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. As the clinical relevance of this finding for human is questionable, the applicant as a follow-up measure will perform post-marketing studies with measurements of ACTH and cortisol.

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. This is mentioned in the SPC section 5.3.

Specific dependence studies performed in rats and monkeys suggest that aripiprazole does not have significant abuse liability.

4. Clinical aspects

Introduction

The proposed indication of aripiprazole is the treatment of schizophrenia.

A total of 34 clinical pharmacology studies included results from healthy subjects (24 studies), patients with schizophrenia or schizoaffective disorder (6 studies), and one study each in patients with hepatic impairment, renal impairment, elderly patients with dementia, and children/adolescents with conduct disorder. In addition, 17 Phase I, II and III clinical studies were conducted in Japan. As they are significantly different (design, strength etc.) from the other studies of the aripiprazole clinical program, their results have been used where appropriate and kept separate from the safety database.

Clinical pharmacology

Pharmacodynamics

- **Mechanism of action**

Observations on the primary pharmacodynamics of aripiprazole suggest that its efficacy is mediated through a combination of partial agonist activity at dopamine D2 receptors and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors

- **Primary and Secondary pharmacology**

The clinical pharmacology development consisted in a single pharmacodynamic study (Study 31-94-201) and a pharmacodynamic interaction study between aripiprazole and alcohol (Study 31-00-230). Further to these, the pharmacokinetic studies produced data on safety and tolerability.

PET scanning conducted study 31-94-201 to determine the degree of brain D2 receptor occupancy induced by aripiprazole. A dose-dependent increase in dopamine D_2 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, is 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 affect 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 SPC, concomitant intake of alcohol with aripiprazole is not recommended.

Pharmacokinetics

- **Bioavailability/Bioequivalence**

All studies complied with current standards of laboratory, clinical and biostatistical practices.
The absolute oral and IM bioavailability of aripiprazole have been established to be 0.870 and 1.01, respectively. This indicates that aripiprazole is nearly completely absorbed and undergoes minimal pre-systemic metabolism, with peak concentrations occurring 3-5 h after dosing.

The applicant showed bioequivalence between the 15 mg and 3x5 mg tablets (CN138-035).

Bioequivalence between the reference commercial tablet (anhydrous aripiprazole) and two prototypes containing 20-30% and 100 % respectively of the monohydrate form was established. A further study established also the bioequivalence of the 30 mg and 3x10 mg tablets.

The rate and extent of absorption complied with usual bioequivalence criteria for fed (high fat breakfast) and fasted states. Therefore, no recommendation with respect to food intake as related to drug administration has been considered necessary.

- **Distribution**

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.

- **Metabolism and Elimination**

Aripiprazole is primarily metabolized by CYP3A4 and CYP2D6 isozymes. OPC-14857 produced by dehydrogenation of the quinolinone ring is the major active metabolite in plasma.

OPC-3373, product of N-dealkylation, is a main urine metabolite and DM-1451, product of a monohydroxylation of the aromatic ring, is mainly eliminated in the faeces. Some of these primary metabolites undergo subsequent biotransformation: N-dealkylation, hydroxylation and glucuronide or sulfate conjugation.

The mean terminal half-life of aripiprazole is 75 h after 5 -15 mg oral dose and 99 h following a 2 mg i.v. dose, the steady-state volume of distribution is 4.94 L/kg and the total body clearance is 0.72 mL/min/kg and primarily hepatic.

Daily administration of 5, 10, 15 and 20 mg of aripiprazole achieved steady-state concentrations within 14 days of dosing. An accumulation index (ca) of 2.8 and a fluctuation index of 43 to 55% were observed.

- **Dose proportionality and time dependencies**

Aripiprazole exhibits linear pharmacokinetics within the 5-30 mg dose range.

There are no clinically significant differences between morning and evening administration.

The inter-subject variability of Cmax and AUC of aripiprazole ranges from 16 to 60% and the intra-subject variability from 7 to 18% expressed as relative standard deviation.

- **Special populations**

Gender and age differences (independently of disease) do not provide evidence for the need to dose adjustment. Results of a population pharmacokinetics and pharmacodynamics study using NONMEM support the general conclusion from the individual interaction and special population studies that no dose adjustments are needed based on demographic variables

A study of subjects with severe renal impairment did not show any effects on aripiprazole PK values. A study on the effect of severe hepatic impairment did not reveal significant PK changes, but the number of subjects with severe liver disease was to small to draw definitive conclusions.

In summary, the main pharmacokinetic characteristics are shown in the table below:

Bioavailability	Oral: 87% - IM : 101%
T1/2 – Tmax-ss	75h to 146h (extensive and poor CYP2D6 metabolisers) - Tmax 3-5h
Cmax - AUC	AUC $_{0-\infty}$ ≈ 3500 µgh/L – Cmax ≈ 55 µg/L for 15 mg single dose
Linearity	Linear PK between 5-30mg for 7 days Accumulation index:2.8 at steady state (14 days)
Effect of food	No interaction
Distribution	Vss=4.94L/kg; protein binding >99%
Metabolism	CYP3A4 and CYP2D6 (substrate) Main metabolites:OPC-14857 (active), OPC-3373, DM-1452 & DCPP
Elimination	Total radioactivity: 27% in urine and 60% in faeces Unchanged aripiprazole <1% in urine and ≈ 18% in faeces Total body clearance 0.7 ml/min/kg, primarily hepatic
Special populations	No evidence of effects in renal and hepatic impaired patients
Gender/age effect	No significant effects

- **Interaction studies**

Due to the aripiprazole complex metabolic pattern, involving CYP3A4 and CYP2D6 isozymes several interactions are expected. This is reflected in the SPC.

In a clinical study with healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was not changed. The AUC and C_{max} 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 C_{max} by 63% and 37% respectively. The AUC and C_{max} 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 C_{max} 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 C_{max} and AUC after carbamazepine co-administration were 69% and 71% lower, respectively, than those following aripiprazole alone treatment.

Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects.

Recommendation on the dosage adjustment of aripiprazole in case of co-administration or discontinuation of the above enzymes inducers or inhibitors is given in the SPC (4.5).

When either valproate or lithium was 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.

The H2 antagonist famotidine, a gastric acid blocker, reduces aripiprazole rate of absorption but this effect is deemed not clinical relevant.

Activated charcoal was found to be a potential useful treatment for aripiprazole overdose.

Clinical efficacy

The aripiprazole clinical program for schizophrenia consisted of five short-term Phase II/III studies, six long-term studies and five special studies. Ten additional Phase II/III efficacy studies were conducted in Japan.

Among the 5 short-term (4 to 6 weeks) phase II/III studies, two-phase II studies support efficacy: 31-93-202 (an ascending-dose study) and 31-94-202 (a fixed-dose study). Three Phase III studies are considered key (pivotal) efficacy studies: 31-97-201 and 31-97-202 (4-week fixed-dose studies, each with an active control) and CN138-001 (a 6-week, fixed-dose study). The studies were all multi-center, randomized, double blind, and placebo-controlled. Haloperidol was the active control in three studies (31-93-202, 31-94-202 and 31-97-201) and risperidone was used in one (31-97-202). At the conclusion of the short-term studies, eligible patients were given the option of continuing on long-term treatment, either in the extension phase of the protocol that the patient had completed (for patients in Study CN138-001) or in an open-label long-term study.

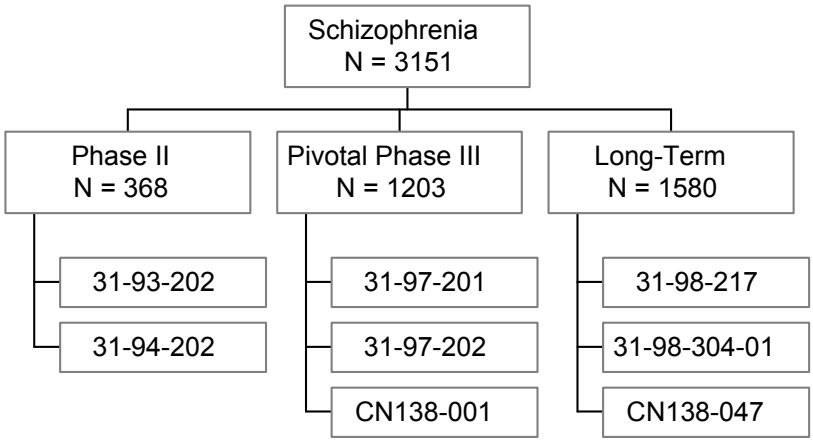
Among the 6 long-term (26-52 weeks) studies, two double blind, active-controlled, long-term studies, 31-98-217 and 31-98-304-01, enrolled patients who had not previously participated in an aripiprazole study. The two studies were prospectively designed to be analysed together. These studies were 52 weeks in duration and assessed maintenance of efficacy versus haloperidol. Study CN138-047 was a long-term 26-week, double blind, placebo-controlled study providing information on long-term maintenance treatment. Study CN138-002 was a 26-week double blind, active-controlled trial to compare safety and tolerability of aripiprazole and olanzapine as evidenced by weight gain during treatment.

The applicant considers that the two additional studies should only be evaluated for safety: 31-98-213, because of its open-label design, and 31-97-301 because it was terminated early due to unsatisfactory dissolution tests of overencapsulted (blinded) tablets of haloperidol.

The five special studies are an heterogeneous group: 2 are efficacy studies in populations different from the target population, namely elderly patients with dementia (Study 31-98-203) and elderly patients with psychosis in Alzheimer's dementia (study CN138-006). The other three (studies 31-98-202, 31-99-224 and 31-98-215) are 2 dose-finding studies and a dose switching study based on safety parameters rather than on efficacy.

Study 31-98-202 was later invalidated due to non-compliance with GCP.

The diagram below summarises the most pertinent efficacy studies:



Short-Term Studies (≤ 6 Weeks)

Phase II dose-ranging studies

Study 31-93-202: Efficacy and Tolerability of Ascending Doses of aripiprazole (5 mg to 30 mg) Compared to Placebo and to Haloperidol (5 mg to 20 mg) in Acutely Relapsing Hospitalised Schizophrenic Patients.

The primary objective of the study was to assess the efficacy of aripiprazole (aripiprazole) for the treatment of acute schizophrenia and the tolerability of the effective doses.

This was a randomized, multicentre, double-blind, placebo-controlled, parallel group, in-patient, 4-week study of ascending doses of aripiprazole in acutely relapsing schizophrenic (Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM-IV) criteria) male and female patients with a history of responding to antipsychotic drugs.

A total of 103 patients were randomised: 34 in the aripiprazole group, 34 in the haloperidol group, and 35 in the placebo group. A total of 53 patients completed the study: 21 in the aripiprazole group, 20 in the haloperidol group and 12 in the placebo group. The rate of dropouts was 49% (the estimative for sample size calculations was 30%).

Data on the primary of efficacy endpoints (change from baseline to the last visit in the BPRS-total score and number of patients with a reduction of at least one point from baseline to last visit in the CGI-severity score) are presented in the table below. The secondary determination of efficacy was based on the change in score on the PANSS from baseline to the last visit. Responder rates and CGI Efficacy Index were also examined.

Aripiprazole was found to be effective and generally well tolerated at a maximum dose of 30 mg/day. Aripiprazole showed some level of efficacy as measured by improvement in all illness severity scores (BPRS-total, BPRS-core, CGI-severity, CGI-improvement, and PANSS-total) prominently after 2 weeks (escalation period). The responder rates of aripiprazole compared to placebo was statistically significant (p=0.035) with regard to CGI-severity score.

Table 31-93-202-BPRS total score

	Estimated treatment effect	p-value	Lower 95% confidence limit	Upper 95% confidence limit
Aripiprazole vs pl	**-6.25**	**<0.02**	**-11.21**	**-1.29**
Haloperidol vs pl	**-6.41**	**<0.01**	**-11.12**	**-1.70**

Table 31-93-202 –one point improvement in CGI severity score.

Treatment group	N	Nº responders	% of responders	Treatment comparision	p-value
aripiprazole	**33**	**14**	**42.4**	**Ari vs pl**	**p=0.035**
haloperidol	**33**	**18**	**54.5**	**Hal vs pl**	**p=0.003**
placebo	**35**	**7**	**20.0**		

Study 31-94-202: A Dose Ranging Study of the Efficacy and Tolerability of aripiprazole in Acutely Relapsing Hospitalised Schizophrenic Patients

The primary objective of the study was to determine the original dose of aripiprazole for the treatment of acute schizophrenia. This was a randomized, multicenter, double-blind, placebo-controlled, parallel-group, in-patient, 4-week study of the efficacy and tolerability of three doses of aripiprazole: 2 mg, 10 mg and 30 mg.

The primary determination of efficacy was based on a comparison of aripiprazole treatment groups versus placebo for: (1) psychotic items subscale of the Brief Psychiatric Rating Scale (BPRS-score) change from baseline to last visit, and (2) Clinical Global Impression (CGI)-improvement at last visit.

The aripiprazole-30 mg group only was significantly superior to placebo at the last visit for the primary endpoints of BPRS-core score (p=0.003) and CGI-improvement (p=0.0004).

The following table summarises the results in the primary variables

Table 31-94-202–primary end-points

Variable	Treatment comparision	Estimated treatment effect	p-value	Lower 95% confidence limit	Upper 95% confidence limit
BPRS core	**Arip 2mg vs pl**	**-1.31**	**ns**	**-2.93**	**0.31**
	Arip 10mg vs pl	**-0.76**	**ns**	**-2.40**	**0.87**
	Arip 30mg vs pl	**-2.21**	**<.01**	**-3.82**	**-0.60**
	Hal 10mg vs pl	**-2.26**	**<.01**	**-3.86**	**-0.66**

Table 31-94-202–primary end-points

Variable	Treatment comparision	Estimated treatment effect	p-value	Lower 95% confidence limit	Upper 95% confidence limit
CGI-improvement	**Arip 2mg vs pl**	**-0.41**	**ns**	**-0.95**	**0.13**
	Arip 10mg vs pl	**-0.56**	**<0.05**	**-1.11**	**- 0.02**
	Arip 30mg vs pl	**-0.97**	**<0.01**	**-1.51**	**- 0.44**
	Hal 10mg vs pl	**-0.59**	**<0.05**	**-1.12**	**- 0.06**

Overall, based on these 2 Phase II studies, the only dose of aripiprazole that clearly differentiate from placebo is 30 mg. Therefore it is uncertain if this is the minimal effective dose or the optimal dose.

Phase III, short-term, placebo-controlled studies

Three Phase III studies are considered key efficacy studies: 31-97-201 and 31-97-202 (4-week fixed-dose studies, each with an active control) and CN138-001 (a 6-week, fixed-dose study). The studies were all multi-center, randomized, double-blind, and placebo-controlled.

Study 31-97-201: A Phase III, Double-Blind, Placebo-Controlled Study of Aripiprazole in the Treatment of Psychosis

The objectives of this study were to compare the safety and efficacy of two doses of aripiprazole (15 mg and 30 mg) versus placebo for the treatment of acute psychosis (in schizophrenia and schizoaffective disorder), and to evaluate the efficacy of aripiprazole on the negative symptoms of psychosis and the relationship of aripiprazole doses with time to response.

This study was a multicenter, 4-week, randomized, double blind, parallel group comparison of the safety and efficacy of aripiprazole, haloperidol 10 mg, and placebo. Approximately 400 patients who were in acute relapse with a diagnosis of schizophrenia or schizoaffective disorder, and who had previously responded to neuroleptics were to be enrolled in the study. The total number dropouts was 40%.

The aripiprazole 15-mg group showed significantly greater improvement at endpoint compared with the placebo group on all efficacy measures (the mean change from baseline in the PANSS Total Score, PANSS Positive and CGI Severity of Illness Score as primary endpoints, PANSS Negative Subscale Scores, and the percentage of responders as secondary endpoints) including a significant difference from the placebo group in time-to-response analysis for the CGI Improvement Score ($p = 0.0122$). Patients in the aripiprazole 30-mg group also improved similarly than the 15 mg group compared to placebo group.

Study 31-97-202: A Phase III, Double Blind, Placebo-Controlled Study of Aripiprazole in the Treatment of Psychosis, with Risperidone as Active Control

The objectives of this study were to compare the safety and efficacy of 20-mg and 30-mg aripiprazole versus placebo for the treatment of acute psychosis (in schizophrenia and schizoaffective disorder). In addition, information was gathered on the efficacy of aripiprazole on the negative symptoms of psychosis and the relationship of aripiprazole doses with time to response.

This study was a multicenter, 4-week, randomized, double blind, parallel-group comparison of the safety and efficacy of aripiprazole, risperidone 6 mg, and placebo. Approximately 400 patients who were in acute relapse with a diagnosis of schizophrenia or schizoaffective disorder, and who had previously responded to neuroleptics were to be enrolled in the study.

Primary efficacy measures where based on mean change from baseline in the PANSS Total Score, PANSS Positive Subscale Score and CGI Severity of Illness Score. Secondary endpoints where measured on PANSS Negative Subscale Score, the mean CGI Improvement Score, mean change from baseline in the PANSS-Derived BPRS Core Score, and the percentage of responders.

Of the 404 randomized patients, 289 had a diagnosis of schizophrenia and 115 had a diagnosis of schizoaffective disorder. Of the 289 patients with schizophrenia, 78 were randomized to the placebo group, 74 to the risperidone group, 66 to the aripiprazole 20-mg group, and 71 to the aripiprazole 30-mg group; 289 were included in the Safety Sample and 282 in the Efficacy Sample. One hundred eighty-three (60%) of the 289 randomized patients with a diagnosis of schizophrenia completed the study.

Both the aripiprazole 20-mg group and the aripiprazole 30-mg group, as well as risperidone 6 mg, showed significantly greater improvement at endpoint compared with the placebo group on all efficacy measures.

Study CN 138-001: A Multicenter, Randomized, Double-blind, Placebo-controlled Study of Three Fixed Doses of Aripiprazole in the Treatment of Patients with Acute Schizophrenia

The primary objective of this study was to compare the efficacy of three fixed doses of aripiprazole (10, 15 and 20 mg) with placebo in the treatment of acutely relapsed patients with a diagnosis of schizophrenia.

The secondary objective of this study was to compare the safety of three fixed doses of aripiprazole with placebo in the treatment of acutely relapsed patients with a diagnosis of schizophrenia

This study was a multicenter, randomized, double-blind, placebo-controlled trial with four parallel groups of inpatients. The total number of dropouts was 66%.

All three aripiprazole treatment groups showed statistically significantly greater improvement than placebo for the PANSS Total Score (the primary endpoint). The number of responders for CGI scores (a secondary endpoint) was statistically superior to placebo aripiprazole in the 20-mg group.

The table below summarizes the PANSS total score for the 3 studies:

PANSS Total Score; Model-Based Mean Change from Baseline at Endpoint; LOCF Data Set, Efficacy Sample; Key Phase III, Short-Term, Placebo-Controlled Efficacy Studies for Schizophrenia

	PANSS Total Score				
Protocol/ Treatment	**N**	**Baseline**	**Change from Baseline**	**Treatment Difference (95% CI) versus Placebo**	**P-Value**
31-97-201 (4-week study)					
Placebo	102	100.9	-2.9	--	--
Haloperidol 10 mg	99	99.9	-13.8	-10.8 (-17.2, -4.5)	0.0008
Aripiprazole 15 mg	99	98.8	-15.5	-12.6 (-18.9, -6.3)	0.0001
Aripiprazole 30 mg	100	99.6	-11.4	-8.5 (-14.7, -2.2)	0.0089
31-97-202 (4-week study)					
Placebo	103	94.1	-5.0	--	--
Risperidone 6 mg	95	92.6	-15.7	-10.7 (-16.6, -4.9)	0.0004
Aripiprazole 20 mg	98	93.5	-14.5	-9.6 (-15.4, -3.8)	0.0013
Aripiprazole 30 mg	96	91.6	-13.9	-8.9 (-14.8, -3.1)	0.0029
CN138-001 (6-week study)					
Placebo	107	92.6	-2.3	--	--
Aripiprazole 10 mg	103	92.9	-15.0	-12.7 (-19.0, -6.4)	0.0001
Aripiprazole 15 mg	103	92.4	-11.7	-9.4 (-15.7, -3.1)	0.0036

PANSS Total Score; Model-Based Mean Change from Baseline at Endpoint; LOCF Data Set, Efficacy Sample; Key Phase III, Short-Term, Placebo-Controlled Efficacy Studies for Schizophrenia

	PANSS Total Score				
Protocol/ Treatment	**N**	**Baseline**	**Change from Baseline**	**Treatment Difference (95% CI) versus Placebo**	**P-Value**
Aripiprazole 20 mg	97	91.9	-14.4	-12.1 (-18.5, -5.7)	0.0002

DISCUSSION ON THE EFFICACY IN THE PIVOTAL SHORT-TERM TRIALS

All the patients enrolled in the 3 pivotal studies were diagnosed according to the criteria of DSM-IV for schizophrenia and related psychotic disorders. In these trials all patients enrolled (n =1203) had an acute relapse also defined according to DSM-IV criteria. All 3 trials were well-controlled, multicenter, appropriately dimensioned and enrolling patients well diagnosed. PANSS total score ranged between 91 and 97 across dose groups. The CGI severity scale had a consistent median score of 5 (marked ill) across all dose groups. Approximately 80% of the patients had a diagnosis of schizophrenia. Most of the patients with schizophrenia had the subtype of paranoid schizophrenia or undifferentiated schizophrenia. In fact only the 6 weeks trial enrolled a "clean" schizophrenia population. Nevertheless the large majority of the patients studied are schizophrenic making the trials valid to draw conclusions on the claimed indication.

These trials have incorporated a short placebo run-in period (2 to 5 days). Two of them had a too short follow-up period (4 weeks) when the standard recommendation is 6 weeks. Furthermore the only trial that fulfils the recommended duration of follow-up has a quite high rate of dropouts 66%.

The results of the 3 short-term pivotal trials are consistent in showing a significant effect of aripiprazole as compared to placebo in the primary end-points, namely PANSS total score, the PANSS positive subscore scale and the CGI severity score.

The effects found in the secondary end-points as well as in responders analysis back the primary efficacy analysis. Furthermore the effect size of aripiprazole is numerical similar to the active comparators used: haloperidol 10 mg and risperidone 6 mg.

Important, however, is the fact that the aripiprazole doses used in these trials – 10, 15, 20 and 30 mg are not well discriminated by effect size. The CPMP acknowledge that the trials were not powered to allow inter-dose comparisons but numerical effects sizes produced by these different doses are not increasing as one would expect in a dose dependent process. This fact induces concern because the dose-finding studies did not produce clear-cut results either.

The CPMP considers that aripiprazole (10 to 30 mg) was proven efficacious in the short-term treatment of acute relapses in schizophrenia patients. However the optimal dose was not established.

LONG TERM CONTROLLED STUDIES (> 26 WEEKS)

The long term program consisted of one 26-week placebo-controlled study **(CN138-047)** and two (up to 52-week) haloperidol-controlled studies **(31-98-217 and 31-98-304-01).** The later two studies had nearly identical protocols and were prospectively designed to be analyzed as one study. Patients had not previously been enrolled in an aripiprazole study.

Study 31-98-217/304-01

The primary efficacy variable in this study was the **"time to failure to maintain response"** in responders.

- **Failure to maintain response** was defined as (1) a CGI Improvement Score of 6 or 7 in two consecutive evaluations 3 to 5 days apart, **or** (2) adverse event of worsening schizophrenia (including hospitalisation due to worsening schizophrenia), **or** (3) a score of 5 (moderately severe), 6 (severe), or 7 (extreme) in at least one of the four items of the psychotic subscale of the PANSS (i.e., delusions, conceptual disorganization, hallucinatory behaviour and suspiciousness) in two consecutive evaluations 3 to 5 days apart. Of the two evaluations, the

time-point of the first evaluation was used for determination of failure to maintain response. For patients who had missing data in the second follow-up evaluation to confirm failure to maintain response, the Last Observation Carried Forward (LOCF) imputation method was used and these patients were considered to have failed.

- **Response was defined** as a ≥20% decrease from baseline in PANSS Total Score and, at the same visit, the patient did not meet any of the above three failure criteria.

Secondary efficacy variables were: 1) change from baseline in PANSS Total Score, 2) change from baseline in PANSS Positive Subscale Score, 3) change from baseline in PANSS Negative Subscale Score, 4) change from baseline in CGI Severity of Illness Score, 5) CGI Improvement Score as recorded, 6) change from baseline in MADRS Total Score, 7) Time to first response, 8) Time from first response to failure to maintain response, 9) Time to discontinuation due to lack of response to study drug, 10) Time to discontinuation due to lack of response to study drug or adverse event.

The discontinuation rate observed in the study was 57% in the aripiprazole group and 70% in the haloperidol group.

Results on the primary efficacy parameter (time to failure to maintain response in responders). No difference was seen between aripiprazole and haloperidol 10 mg. In a supportive analysis, the time to failure in all randomized patients showed a positive trend favoring aripiprazole over haloperidol ($p = 0.084$). A second supportive analysis, the percentage of patients still receiving treatment and in response at Weeks 8, 26, and 52, significantly favoured aripiprazole ($p \leq 0.005$ at all weeks). Both were prospectively defined as key supportive analyses of the primary analysis and are clinically relevant.

These results are summarized in the following table:

Key Efficacy Results; LOCF Data Set; Long-Term, Active-Controlled Efficacy Studies for Schizophrenia (31-98-217 and 31-98-304-01)

Variable	Haloperidol	Aripiprazole	P-Value
Number of patients in Randomized Sample	433	861	--
Number of patients in Efficacy Sample	430	853	--
Number (%) Responders	298 (69%)	610 (72%)	0.362
Primary Analysis (Time to failure in Responders)			
Hazard Ratio (95% CI) (aripiprazole: haloperidol)	0.881 (0.645 - 1.204)		0.4271
Number (%) of failures	58 (19%)	125 (20%)	--
Proportion[a] (S.D.) of patients not yet failed			
Week 8	93.0 (1.5%)	91.7 (1.1%)	--
Week 26	81.1 (2.6%)	83.5 (1.6%)	--
Week 52	73.3 (3.1%)	77.4 (1.8%)	--
Hazard Ratio (95% CI) (aripiprazole : haloperidol)	0.858 (0.721 - 1.021)		0.0839
Number (%) of failures	193 (45%)	376 (44%)	--
Proportion (S.D.) of patients not yet failed			
Week 8	68.5 (2.3%)	71.4 (1.6%)	--
Week 26	55.6 (2.6%)	59.8 (1.7%)	--
Week 52	49.2 (2.7%)	54.0 (1.8%)	--
Supportive Analysis #2			
On-treatment and in response (N [%])[b]			
Week 8	192 (44%)	449 (52%)	0.005
Week 26	145 (33%)	380 (44%)	< 0.001
Week 52	117 (27%)	343 (40%)	< 0.001

a Kaplan-Meier estimates.
b The denominator is the number randomized.

Secondary Efficacy Results: Aripiprazole was statistically superior to haloperidol as determined by the time to discontinuation due to either lack of response to study drug or adverse event ($P < 0.001$). The risk ratio for this event was 0.692 (95% CI: 0.573 - 0.837) indicating that the risk of discontinuation due to either lack of response to study drug or adverse event was 31% lower for the aripiprazole treated patients relative to the patients treated with haloperidol.

Other secondary time-to-event variables included in this study were time to first response (all randomized patients), time to discontinuation due to lack of response to study drug (all randomized patients), and time from first response to failure to maintain response (responders only). No statistically significant differences were observed between the two treatment groups in these variables.

Aripiprazole showed significant improvement over haloperidol in the treatment of negative and depressive symptoms. The improvement in treatment of negative symptoms was demonstrated by significant differences in the comparison of mean change from baseline in the PANSS Negative Subscale Score at Weeks 26 (P = 0.029) and 52 (P = 0.011) based on the LOCF data set. The improvement in treatment of depressive symptoms was demonstrated by statistical differences in the comparison of mean change from baseline in MADRS Total Score at Weeks 8 (P = 0.027), 26 (P = 0.022), and 52 (P = 0.031) (LOCF data set).

Study CN138-047: A Multicenter, Randomized, Double-Blind, Placebo Controlled, 26 Week Study of a Fixed Dose of Aripiprazole (15 mg) in the Treatment of Stabilized Patients with Chronic Schizophrenia

The primary objective of this study was to compare the time to relapse from randomization of patients receiving 15 mg of aripiprazole versus placebo over a minimum of 26 weeks in the treatment of stabilized patients with chronic schizophrenia, as measured by Clinical Global Impression of Improvement (CGI-I) score or change in PANSS Total score.

The primary research hypothesis – primary endpoint: time to relapse from randomization- was that stabilized patients with chronic schizophrenia in the placebo group would relapse sooner than patients in the aripiprazole 15-mg treatment group. Relapse was defined as one or more of the following: (1) a CGI-I Score of ≥ 5 (minimally worse), or (2) a PANSS Total Score of ≥ 5 (moderately severe) on the items of hostility or uncooperativeness on 2 successive days, or (3) a ≥ 20% increase in the PANSS Total Score.

Secondary efficacy measures were: 1) number of relapses, 2) time to relapse or discontinuation due to lack of efficacy, 3) time to relapse or to discontinuation due to lack of efficacy or to adverse event (AE), 4) mean change from baseline in the PANSS Total Score, PANSS Positive Subscale Score, PANSS Negative Subscale Score, and the PANSS-Derived BPRS Core Score, 5) mean CGI-I Score, and 6) mean change from baseline in the CGI Severity of Illness Score. These secondary objectives were to assess the efficacy, safety, and tolerability of aripiprazole relative to placebo in the treatment of stabilized patients with chronic schizophrenia.

The discontinuation rate was 54% in the aripiprazole group and 71% in the placebo.

Compared to placebo, 26 weeks of treatment with aripiprazole 15 mg once daily significantly reduced the incidence of relapse of acute schizophrenia. At Week 26, 62.6% of the aripiprazole-treated patients had not relapsed relative to 39.4% of patients randomized to placebo. Aripiprazole treatment was associated with a 50% reduction in the risk for relapse compared to placebo.

On the PANSS Total Score aripiprazole was significantly better than placebo starting at Week 6 and continuing to the end of the study. Given the design of the study this suggests that it is possible to switch stable schizophrenic patients to aripiprazole without worsening the underlying condition.

A summary of efficacy results for the LOCF data set is shown in the following table.

Table CN-138-047: Summary of Efficacy Results for Study CN138-047; LOCF Data Set, Efficacy Sample

	Treatment Group		
Variable	**Placebo N = 149**	**Aripiprazole N = 148**	**Aripiprazole vs. Placebo RR (95% CI)**
PRIMARY EFFICACY ENDPOINT			
Time to Relapse			
Estimated Survival Rate (%)[a] (S.E.)	39.4 (4.24)	62.6 (4.22)	0.50** (0.35, 0.71)
SECONDARY ENDPOINTS			
Number of Relapses			
N (%)	85 (57)	50 (34)	0.59** (0.45, 0.75)
(S.E.)	(4.07)	(3.90)	

Table CN-138-047: Summary of Efficacy Results for Study CN138-047; LOCF Data Set, Efficacy Sample

Variable	Treatment Group: Placebo N = 149	Aripiprazole N = 148	Aripiprazole vs. Placebo RR (95% CI)
Time to Relapse or to Discontinuation Due to Lack of Efficacy			
Estimated Survival Rate (%)[b] (S.E.)	39.4 (4.24)	62.6 (4.22)	0.50** (0.36, 0.72)
Time to Relapse or to Discontinuation Due to Lack of Efficacy or to AE			
Estimated Survival Rate (%)[b] (S.E.)	38.1 (4.17)	58.8 (4.22)	0.56** (0.40, 0.78)
PANSS Total Score			
Mean Baseline (N)	83.12 (147)	81.22 (146)	-1.90 (-4.01, 0.21)
Mean Change at Week 6 (N)	1.78 (147)	-2.04 (146)	-3.82* (-7.18, -0.45)
Mean Change at Week 26 (N)	4.50 (147)	-2.08 (146)	-6.59** (-10.77, -2.40)
PANSS Positive Subscale Score			
Mean Baseline (N)	17.47 (147)	17.48 (146)	0.01 (-0.78, 0.80)
Mean Change at Week 6 (N)	1.23 (147)	-0.04 (146)	-1.27* (-2.33, -0.21)
Mean Change at Week 26 (N)	2.37 (147)	0.12 (146)	-2.24** (-3.54, -0.95)
PANSS Negative Subscale Score			
Mean Baseline (N) (S.E.)	23.72 (147) (0.33)	23.13 (146) (0.33)	-0.58 (-1.43, 0.27)
Mean Change at Week 6 (N) (S.E.)	-0.78 (147) (0.30)	-1.04 (146) (0.31)	-0.27 (-1.06, 0.52)
Mean Change at Week 26 (N) (S.E.)	-0.54 (147) (0.41)	-1.40 (146) (0.41)	-0.85 (-1.91, 0.21)
PANSS-Derived BPRS Core Score			
Mean Baseline (N) (S.E.)	11.52 (147) (0.22)	11.39 (146) (0.22)	-0.12 (-0.68, 0.43)
Mean Change at Week 6 (N) (S.E.)	0.56 (147) (0.27)	-0.27 (146) (0.26)	-0.83 (-1.50, -0.15)
P-value	$0.01 < p \leq 0.05$		
Mean Change at Week 26 (N) (S.E.)	1.17 (147) (0.33)	-0.21 (146) (0.32)	-1.37 (-2.20, -0.54)
P-value	≤ 0.01		
CGI Severity of Illness Score			
Mean Baseline (S.E.)	3.55 (0.03)	3.49 (0.03)	-0.05 (-0.14, 0.03)
Mean Change at Week 6 (S.E.)	0.20 (0.06)	0.06 (0.06)	-0.15 (-0.30, 0.01)
Mean Change at Week 26 (S.E.)	0.40 (0.07)	0.15 (0.07)	-0.25 (-0.44, -0.06)
P-value	$0.01 < p \leq 0.05$		
CGI Improvement Score			
Mean at Week 6 (S.E.)	4.13 (0.10)	3.69 (0.10)	
P-value	≤ 0.01		
Mean at Week 26 (S.E.)	4.48 (0.11)	3.77 (0.12)	
P-value	≤ 0.01		

DISCUSSION ON THE EFFICACY IN LONG-TERM TRIALS

Trials 31-98-217/304-01 used aripiprazole in a targeted dose of 30 mg/d and compared it to haloperidol 10 mg. Initially, the trials were designed as a superiority comparison, expected to provide sufficient statistical power to detect a difference between aripiprazole and haloperidol in the rate of maintenance of response (i.e. not failing) at 52 weeks and in the mean changes in PANSS total score at 8 weeks. As no statistical difference between arms was observed, maintenance therapy is not firmly established. Another potential problem is that response has a clear operative definition but no clear timeframe to be assessed. In this context it is a moving targeted that can happen at 4 weeks but also, theoretically, at 26 weeks. The operational definition of response itself is not very stringent because it postulates only 20% improvement in PANSS total score.

However, the trials provide long-term data obtained in randomised, double blind conditions. Haloperidol 10 mg is an acceptable comparator. There is no signal that this comparator had performed particularly bad in these trials. The number of responders in both groups was high 69% for haloperidol and 72% for aripiprazole. These high rates can however be an indicator that the definition of responder was not indeed too stringent. In any case the rates are numerically similar. At end-point 52 w the rates of maintenance of response are also high and numerically alike 73.3% for haloperidol and 77.4% for aripiprazole. Further more the completion rate is significantly higher for patients on aripiprazole

(43%) than for haloperidol (30%). This difference is at cost of a lower rate of discontinuation due to adverse events other than worsening of schizophrenia. It is also important to note that discontinuations due to insufficient clinical response were low: haloperidol 9% and aripiprazole 7%.

In addition, study CN138-047could help supporting the maintenance therapy claim, as this study is a kind of relapse prevention study placebo controlled although it does not include the acute treatment phase and starts with stable patients. The dose of aripiprazole in this trial was 15 mg. At 6 months the relapse rate was 37.4% for the aripiprazole group and 60.6% for the placebo group ($p<0.01$).

Unfortunately, the issue of finding the best-recommended dose was not addressed properly and the long-term trials are illustrative: one uses 30 mg and the other 15 mg.

Concerns were raised by CPMP regarding the design of the long-term studies for the demonstration of the long-term efficacy on the maintenance of the acute antipsychotic effects of aripiprazole.

The applicant was asked to explain or clarify issues such as (1) the differences in the definitions of failure to maintain response in the 52-weeks trial and for relapse in the 26 weeks trial. Furthermore it was noted that the definition included "worsening of schizophrenia" as an AE. There were doubts about how this was counted in the actual analysis, (2) the design of the long-term trial in relation with the lack of time frame for the occurrence of a defined response, in order to allow meaningfulness to the primary end-point – time to failure maintenance of response, (3) in the 26-weeks relapse prevention study (CM138-047), the inclusion only of stable schizophrenic patients and its relevance for the general schizophrenic population.

The applicant performed analyses for each study (52 weeks and 26 weeks) by using the definition of failure to maintain response from the other study and showed that the results were unchanged.

Further data provided by the company shows that the large majority of responses did occur in the acute phase of the trial (first 8 weeks). In this perspective the data provided by the 52-week trial is not essentially different from the one provided with other atypical antipsychotics.

Regarding the extra analysis done at CPMP request, observed case (OC), LOCF, additional method of imputation (Mixed effects Model Repeated Measures analysis (MMRM)), responders only analysis, all are consistent in showing a positive effect of aripiprazole which is numerically and occasionally statistically superior to haloperidol. These analyses provide support for the relevance of the effect despite the definition of response being set at a reduction of 20% on PANSS.

In the 26-weeks relapse prevention study (CM138-047), aripiprazole showed superiority over placebo. This is important additional data but refers to a particular population and not the usual population (those that were controlled after an acute episode) in which it is important to assess the prevention of relapse and therefore maintenance of effect. Therefore, this trial is considered to be a supportive trial but cannot provide pivotal data because of the target population.

DISCUSSION ON GCP INSPECTIONS

Study 31-98-217/304 was the result of two identical protocols designed to be analyzed together. One protocol was conducted in the USA and the other in Europe, Australia, New Zealand and South Africa. The non-USA protocol was conducted in a large number of centres 80% of which were located in Europe (Western and Eastern). In fact most of the Western European centres (the exception was France) failed to enrol a significant number of patients and the European contribution came mostly from Russia, Poland, Bulgaria and Hungary. The CPMP requested a GCP inspection, as this study concerns a vulnerable psychiatric population and as much of the data comes from countries where GCP inspections for Centralised Procedure applications had not yet been carried out. A number of inspections were carried out at clinical investigator sites, firstly in Estonia and Bulgaria.
This first EMEA inspection found critical findings in 1 of the 2 centres inspected. The important inspection findings pertain to several aspects that threatened the validity of the data, such as dosing, amendments, and monitoring:

1. The initial doses in the trials (aripiprazole 30 mg and haloperidol 10 mg) could be reduced after 1 week during the trial if the patient was considered intolerant. The adjustment of dose was poorly documented at one of the sites inspected. The other site had succeeded in documenting the dose adjustments. The failures related to poor design of the tear-off labels of the study

medication, the CRFs and other forms used to document the dose. If this would have happened in other centers the true dose administered would be impossible to confirm retrospectively

2. The definition of response was amended 3 times during the trial always to loosen its criteria. The last time was just one month before the end of the study. One of the amendments proposed the introduction of "worsening of schizophrenia" as an Adverse Events in the definition. The inspection found a problem in the classification of 2 such Adverse Events at one of the inspected sites.

3. There were concerns about the failure of the company's internal monitoring / audit to detect and resolve the problems in particular in relation to the dose administered

In order to determine which were isolated and which were systematic problems, CPMP requested a re-inspection of the trial, at four additional clinical investigator sites (3 in Russia and 1 in France) and at the CRO responsible for monitoring the trial in Europe. In addition the applicant conducted a comprehensive internal audit of the trial, by an independent third party.

The re-inspection confirmed that there were problems in reconstructing the actual dose administered to patients after the dose adjustment (or whether or not this adjustment took place). Additional concerns were raised about the training of investigators and standardisation of the PANSS assessments, including the use of local language in this regard, although the final PANSS scores were being completed in English, as that is the validated version The answer of the applicant regarding these concerns did not fully resolve the issues raised by the inspectors, but the CPMP considered based on the information assessed that the results of the study could nonetheless be used to support long-term efficacy, when considered in conjunction with other trials.
However, critical discrepancies in the listings of batch numbers in the final study report were uncovered during these inspections, which led to a significant revision by the applicant of listings identifying the batches of product used and taken by the patients during the study. The CPMP remained concerned that the underlying assignment of treatments to patients might have been compromised. Consequently, a GMP inspection was requested for the study 31-98-304-01 in order to review a sample of batch records relating to the packaging processes for the clinical trial materials. The inspection provided assurance that the integrity of the supplies had not been compromised.

Clinical safety

The All Aripiprazole Data Set includes all patients treated with aripiprazole in all Phase II/III studies involving patients with a diagnosis of schizophrenia, bipolar mania, or dementia.

A total of 4947 subjects and patients were exposed to aripiprazole in studies conducted in North America, Europe, and the rest of the world other than Japan; 748 in clinical pharmacology studies and 4199 in Phase II/III studies.
The 4199 patients in the All Aripiprazole Data Set treated with aripiprazole in Phase II/III studies represent 2180 patient exposure years. Of these, 1293 (30.8%) patients were treated with aripiprazole for 6 months or longer. Eight hundred and five (19.2%) patients received aripiprazole for at least 1 year with 238 (5.7%) patients continuing aripiprazole treatment for at least 2 years.

A total of 3476 patients in the All Schizophrenia Data Set were treated with aripiprazole in Phase II/III studies representing 2024 patient exposure years. Of these, 1213 (34.9%) patients were treated with aripiprazole for 6 months or longer. Eight hundred (23.0%) patients received aripiprazole for at least 1 year with 238 (6.8%) patients continuing aripiprazole treatment for at least 2 years.

All four of the fixed-dose design studies were pooled for purposes of assessing treatment related AEs by dose (Table 1). Aripiprazole was similarly tolerated across the entire dose range.

ADRs were considered as reasonably attributable to the drug when they occurred at an incidence of ≥ 1% increase over placebo as well as those that occurred at a lower incidence and were deemed clinically important. ADRs are listed in Table 2.

Table 1: **Incidence of Treatment-Related AEs Occurring in At Least Five Percent of Patients: 31-94-202, 31-97-201, 31-97-202, CN138-001**

	Placebo N (%)	Ari 2 mg N (%)	Ari 10mg N (%)	Ari 15mg N (%)	Ari 20mg N (%)	Ari 30mg N (%)
N = Safety Sample	**378**	**59**	**165**	**207**	**199**	**262**
N with ≥ 1 AE	219(57.9)	35(59.3)	107(64.8)	135(65.2)	137(68.8)	178(67.9)
Body as a Whole						
Headache	45(11.9)	12(20.3)	34(20.6)	30(14.5)	46(23.1)	34(13.0)
Asthenia	16(4.2)	4(6.8)	7(4.2)	9(4.3)	7(3.5)	15(5.7)
Digestive System						
Constipation	19(5.0)	3(5.1)	9(5.5)	10(4.8)	14(7.0)	20(7.6)
Vomiting	20(5.3)	4(6.8)	11(6.7)	11(5.3)	24(12.1)	18(6.9)
Nausea	26(6.9)	2(3.4)	16(9.7)	22(10.6)	31(15.6)	16(6.1)
Dyspepsia	26(6.9)	5(8.5)	20(12.1)	19(9.2)	17(8.5)	13(5.0)
Diarrhea	19(5.0)	1(1.7)	4(2.4)	4(1.9)	11(5.5)	7(2.7)
Nervous System						
Insomnia	36(9.5)	11(18.6)	22(13.3)	30(14.5)	38(19.1)	37(14.1)
Somnolence	27(7.1)	6(10.2)	12(7.3)	17(8.2)	13(6.5)	33(12.6)
Akathisia	17(4.5)	1(1.7)	12(7.3)	12(5.8)	17(8.5)	31(11.8)
Lightheadedness	15(4.0)	4(6.8)	13(7.9)	18(8.7)	22(11.1)	24(9.2)
Anxiety	26(6.9)	0	7(4.2)	20(9.7)	18(9.0)	22(8.4)
Agitation	44(11.6)	1(1.7)	9(5.5)	22(10.6)	22(11.1)	16(6.1)

Table 2: **Adverse Drug Reactions: Placebo-Corrected Incidence (At Least One Percent Greater Than Placebo) in Short and Long-Term Studies**

	Aripiprazole
# Pts in Safety Sample	1079
	%
Body as a Whole	
Headache	4.71
Asthenia	1.17
Digestive System	
Nausea	2.97
Vomiting	2.54
Dyspepsia	2.38
Constipation	2.12
Nervous System	
Lightheadedness	4.98
Insomnia	4.23
Akathisia	3.46
Somnolence	2.51
Tremor	1.46
Special Senses	
Blurred Vision	1.04

*Serious Adverse Events***:** The incidence of SAEs in the all schizophrenia data set is similar to that seen in the all aripiprazole data set. Aside from psychosis which was discussed previously in the efficacy section, no treatment-related SAE occurred at an incidence of ≥ 1%.

*Suicide***:** Suicide is associated with the disease state of schizophrenia. Recent estimates of the completed suicide rate for individuals with schizophrenia range from 10% to 13%. In the all schizophrenia data set, there were ten patients who died as a result of a suicide attempt. The incidence of completed suicide associated with aripiprazole treatment (0.3%) is similar to the incidence reported with other atypical antipsychotics.

*Deaths***:** In the all aripiprazole data set there were 40 deaths. Nineteen patients were elderly patients participating in the 3 studies of psychosis associated with Dementia of the Alzheimer's Type. These studies included patients between 56 - 99 years of age (mean age 81.8 years) and the causes of death in these studies are those typically associated with the advanced age of this population. Of the 21 deaths occurring in schizophrenic patients, none were in the short-term placebo controlled studies. All were determined to be unrelated to study medication with the exception of one suicide death reported to be possibly related to study medication.

Discontinuations Due To Adverse Events: In the all schizophrenia data set, the percentage of patients who discontinued due to AEs was 23.6%, similar to the discontinuation rate in the all aripiprazole data set. The percentage of patients who discontinued for treatment-related AEs was 8.0%. The most frequent treatment-related AE which led to discontinuation, aside from psychosis was akathisia (0.95%).

In the short-term studies, the percentage of patients in the aripiprazole group who discontinued due to AEs was similar to the placebo, haloperidol and risperidone groups. There was no apparent relationship between aripiprazole dose level and the overall incidence of discontinuation due to AEs.

In the double-blind long term studies, the percentage of patients in the aripiprazole groups who discontinued due to AEs was slightly greater than placebo, but lower than haloperidol. A higher percentage of patients in the haloperidol group relative to aripiprazole discontinued treatment due to extrapyramidal syndrome (EPS)-related AEs.

Adverse events by class and special interest:
Specific adverse events associated with the antipsychotic class of drugs include tardive dyskinesia, neuroleptic malignant syndrome (NMS), and seizure. In this class, additional adverse events of special interest include weight gain, QT_c prolongation, hyperprolactinemia, and extrapyramidal syndrome. Although, the specific data related to aripiprazole did not point to such adverse drug reactions, the safety data sets of aripiprazole were specifically investigated in regards to these AEs.

Adverse events associated with antipsychotic class of drug:
Tardive Dyskinesia: The risks of developing tardive dyskinesia, and the potential that it will become irreversible, are believed to increase with the duration of treatment and total cumulative dose. The syndrome can, however, develop after relatively brief treatment periods at low doses. All patients in the schizophrenia clinical studies were at risk for tardive dyskinesia, as a requirement in all studies was response to prior treatment with an antipsychotic agent. In the all aripiprazole data set, the incidence of tardive dyskinesia was 0.38%, and in the all schizophrenia data set the incidence was 0.43%. The treatment-related AE incidence in the all schizophrenia data set was 0.35%. The incidence of first onset of tardive dyskinesia did not increase with exposure to aripiprazole. In the long-term studies, the incidence of tardive dyskinesia in the aripiprazole group was similar to haloperidol.

Neuroleptic Malignant Syndrome (NMS): Neuroleptic Malignant Syndrome, a rare event related to treatment with neuroleptics, is a medical emergency. The incidence of reported NMS during aripiprazole exposure in the all aripiprazole data set was 0.02% (1/4199 patients). One additional patient from a double-blind study in bipolar mania had NMS reported as an AE. However, the reported NMS started 17 days after the last dose of aripiprazole and the patient had initiated therapy with risperidone and haloperidol. The incidence of NMS is below the lower end of the incidence range documented in the literature (i.e., 0.07 - 0.2% in the data from prospective studies)

Seizures: In the all aripiprazole data set, the number of patients with an AE of seizure, grand mal seizure or abnormal EEG was 16 (0.38%). Nine of the 16 patients had confounding factors, such as prior history, concurrent illness, or concomitant medications, that might have contributed to the occurrence of seizure-related AEs.

Other adverse events of special interest:
Extrapyramidal Syndrome (EPS): EPS was assessed by reviewing spontaneous reporting of EPS and EPS-related AEs (dystonia, parkinsonism, akathisia, dyskinetic and residual events), incidence of concomitant medications for the potential treatment of EPS-related AEs, and also in a structured assessment using Simpson-Angus score, Abnormal Involuntary Movement Scale (AIMS) and Barnes Akathisia Global Assessment. The rating scale data corroborates the spontaneously reported AE data.

A summary of the incidence of treatment-emergent EPS-related AEs is presented in table below

Table 23: Percentage of Patients with Treatment-Emergent EPS-Related AEs: Summary of Placebo and Active-Controlled Studies, Safety Sample

	Placebo	Haloperidol	Risperidone	Olanzapine	Aripiprazole
Short-Term Placebo-Controlled Studies (4 - 6 Weeks)					
Short-Term Placebo-Controlled Studies	80/413 (19.4%)	87/200 (43.5%)	30/99 (30.3%)	--	195/926 (21.1%)
Long-Term Comparator Studies					
CN138-002 (26 Weeks)	--	--	--	25/159 (15.7%)	26/155 (16.8%)
31-98-213 (26 Weeks)	--	--	--	16/123 (13.0%)	22/127 (17.3%)
31-98-217 and 31-98-304-01 (52 Weeks)	--	255/431 (59.2%)	--	--	233/859 (27.1%)
CN138-047 (26 Weeks)	20/153 (13.1%)	--	--	--	31/153 (20.3%)
CN138-006 (10 Weeks)	4/102 (3.9%)	--	--	--	5/105 (4.8%)

In the all schizophrenia data set, the incidence of EPS-related AEs was 25.6%, similar to the incidence seen for the all aripiprazole data set. The treatment-related incidence of EPS-related AEs was 21.2%.

In the short-term placebo-controlled studies, the incidence of EPS and EPS-related AEs, for aripiprazole-treated patients (6.0% for EPS and 21.1% for EPS-related AEs) was similar to that of placebo and approximately one-half of the haloperidol group (19.5% for EPS and 43.5% for EPS-related AEs, $p < 0.001$). There was no apparent relationship between the incidence of EPS events and dose. In the long-term controlled studies, the incidence of EPS-related AEs observed for aripiprazole (20.3%) was greater than that of placebo, similar to olanzapine and approximately one-half the frequency seen with haloperidol (59.2%, $p < 0.001$). In general these findings suggest that EPS does not increase with extended exposure to aripiprazole.

QTc Prolongation: QT intervals were read by a central ECG service and corrected for heart rate using the Bazett's formula. The data were analyzed to determine the incidence of QTc prolongation based on the following criteria: > 450 msec from baseline in adult males, > 470 msec for adult females, > 500 msec, increase from baseline ≥ 30 msec and increase from baseline > 60 msec. Means changes in baseline for QTc were also evaluated.

In the short term studies, both the percentage of patients with QTc prolongation and mean change from baseline in QTc were comparable between aripiprazole and placebo. In contrast, risperidone was associated with a significant increase in mean QTc compared to placebo ($p < 0.001$) and a greater proportion of patients with QTc prolongation ($p = 0.048$ for the > 450/> 470 msec parameter). The proportion of patients with an increase in QTc ≥ 30 msec was also significantly greater for haloperidol -($p = 0.026$) and risperidone ($p = 0.001$) compared to placebo. In the long-term studies, for aripiprazole the incidence of QTc prolongation was less than placebo, and less than or equal to that seen for haloperidol.

Effects on Prolactin: Increase in prolactin is associated with the use of conventional antipsychotics, and has been noted with some atypical agents (i.e., high doses of risperidone > 6 mg/day).

For the short-term and long-term controlled studies, patients in the aripiprazole group had median percent decreases from baseline in serum prolactin. In contrast, median percent increases from baseline in serum prolactin were observed for the haloperidol and risperidone groups. In the 52-week controlled study, the median percent change for aripiprazole was significant and lower than that seen for haloperidol.

The prolactin values for the majority of the patients in the aripiprazole group remained within normal limits.

Weight Gain: with regard to weight gain and other metabolic abnormalities, the data indicate that treatment with aripiprazole has a minimal effect on weight and a favorable reduction in serum cholesterol.

Summary on clinical safety

Aripiprazole was in general safe and well tolerated. No deleterious effect on the blood series is apparent; there is no signal that QTc prolongation that might be a clinical relevant problem, the incidence of EPS is globally low in the same range as olanzapine and much lower than haloperidol even lower than risperidone. The mean prolactin levels are decreased what is the opposite to the common effect of antipsychotics that usually increase prolactin. Furthermore aripiprazole do not induce clinically meaningful weight increase.

Orthostatic hypotension was more frequent with aripiprazole than with haloperidol and similar to risperidone. Furthermore nausea and vomiting in long-term were worse for aripiprazole than for haloperidol but in short-term aripiprazole showed an advantage over the comparators. Overall the differences although present are not extremely large. These findings are reported in the SPC.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CPMP opinion there were some unresolved minor quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow up measures within an agreed timeframe.

Non-clinical pharmacology and toxicology

Aripiprazole is a new antipsychotic belonging to the class of atypical antipsychotic drugs. It has been proposed that aripiprazole antipsychotic action could be mediated through a combination of partial agonist at dopamine D2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors. The non-clinical characterization of aripiprazole as a dopamine D2 receptor partial agonist at pituitary lactotrophs predicts a low potential to induce hyperprolactinemia in humans but it may be dose related. Studies on the sedative liability of aripiprazole suggest a reduced sedative potential compared to typical antipsychotics. The safety pharmacology profile of aripiprazole reveals that this agent exhibits a reduced impact on cardiovascular, renal and gastrointestinal systems.

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.

Studies in rats suggest that there is a potential for foetal and neonatal exposure to aripiprazole if administered to pregnant or lactating women. This information is included in section 4.6 of the SPC.

Aripiprazole is primarily metabolized by CYP3A4 and CYP2D6 isozymes. Aripiprazole was mainly eliminated via metabolic clearance and metabolites of aripiprazole were eliminated by both renal and biliary routes in monkeys and humans and predominantly by biliary route in rats.

The gallbladder stone formation observed in monkeys appears to be species specific. The risk of gallstone formation in patients is probably very low since sulfate conjugated metabolites of aripiprazole do not reach sufficient biliary concentrations in humans and since no indication of such a risks occurred during the clinical trials. This is described in the SPC (section 5.3).

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 is 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. As the clinical relevance of this finding for human is questionable, the applicant as a follow-up measure will perform post-marketing studies with measurements of ACTH and cortisol.

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. This is mentioned in the SPC section 5.3.

Specific dependence studies performed in rats and monkeys suggest that aripiprazole does not have significant abuse liability.

Efficacy

The results of the 3 short-term pivotal trials are consistent in showing a significant effect of aripiprazole as compared to placebo in the primary end-points, namely PANSS total score, the PANSS positive subscore scale and the CGI severity score. The effects found in the secondary end-points as well as in responders' analysis back the primary efficacy analysis. Furthermore the effect size of aripiprazole is numerical similar to the active comparators used: haloperidol 10 mg and risperidone 6 mg.

Important, however, is the fact that the aripiprazole doses used in these trials – 10, 15, 20 and 30 mg are not well discriminated by effect size? The CPMP acknowledge that the trials were not powered to allow inter-dose comparisons but numerical effects sizes produced by these different doses are not increasing as one would expect in a dose dependent process. This fact induces concern because the dose-finding studies did not produce clear-cut results either.

The CPMP considers that aripiprazole (10 to 30 mg) was proven efficacious in the short-term treatment of acute relapses in schizophrenia patients. However the optimal dose was not established and the external validity of the results is probably low.

The data on long-term efficacy used aripiprazole in a targeted dose of 30 mg/d and compared it to haloperidol 10 mg. The trial was designed as a superiority trial on rate of maintenance of response at 52 weeks. Although there was no statistical difference between arms, the data available supports that aripiprazole is efficacious for maintenance therapy.

The issue of finding the best-recommended dose was not addressed properly and the long-term trials are illustrative as one uses 30 mg and the other 15 mg.

The recommended daily dose of Abilify is 15 mg although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Safety

As CYP3A4 and CYP2D6 are the primary isozymes responsible for aripiprazole metabolism, the clinical dose of aripiprazole should be adapted when co-administered with potent inducers or inhibitors of these enzymes. This is reflected in the SPC (4.5).

Aripiprazole was in general safe and well tolerated. No deleterious effect on the blood series is apparent; there is no signal that QTc prolongation that might be a clinical relevant problem, the incidence of EPS is globally low in the same range as olanzapine and much lower than haloperidol even lower than risperidone. The mean prolactin levels are decreased what is the opposite to the common effect of antipsychotics that usually increase prolactin. Furthermore aripiprazole do not induce clinically meaningful weight increase.

Orthostatic hypotension was more frequent with aripiprazole than with haloperidol and similar to risperidone. Furthermore nausea and vomiting in long-term were worse for aripiprazole than for haloperidol but in short-term aripiprazole showed an advantage over the comparators. Overall the differences although present are not extremely large. These findings are reported in the SPC.

Benefit/risk assessment

Efficacy. Short-term efficacy for the treatment of schizophrenia acute relapses is established and the recommended dose (dose findings studies failed to discriminate among 15, 20 and 30 mg) for maintenance therapy is not firmly established because the superiority design trial versus haloperidol failed to show superiority. However, the data available backed by the relapse prevention study, despite being done in stable patients and therefore omitting the acute phase and re-randomizations, supports that aripiprazole is efficacious for maintenance therapy. Again there is no good basis to opt between 15 mg and 30 mg.

*Safety***.** The clinical safety profile of aripiprazole do not raises major concerns and has characteristics that compare it to other antipsychotics favourably. The applicant committed in a letter of undertaking to follow up in the clinic, potential hormonal changes of the adrenal gland function within an agreed timeframe.

There is no experience in children or adolescents < 18 years old, as no studies on the safety and efficacy of aripiprazole have been conducted in this population. This is reflected in the SPC (section 4.2)

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk ratio of Abilify in the treatment of schizophrenia was favourable and therefore recommended the granting of the marketing authorisation.