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ASSESSMENT REPORT FOR ABILIFY

International non-proprietary name: (aripiprazole)

Procedure No. EMEA/H/C/000471/II/0048

Variation Assessment Report as adopted by the CHMP with
All information of a commercially confidential nature deleted

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1. Introduction

In general, there is consensus that schizophrenia is a severe psychiatric disorder both in childhood and adolescence as well as in adulthood. The lifetime prevalence of schizophrenia is approximately 1%. It is assumed that only 0.1 to 1% of all schizophrenic psychoses manifest themselves before the age of 10, and 70% of all schizophrenic disorders occur between the age of 20 and 45[1].

The prevalence rate of very early-onset schizophrenia (manifestation before the age of 12) is less than one child in 10,000 children between 2 and 12 years of age[2] . It is estimated that childhood-onset schizophrenia is approximately 50 times less frequent than adult-onset schizophrenia. There is a remarkable increase of schizophrenia after the 13th year of life[3], and the prevalence of schizophrenia among adolescents has been estimated to be as high as 0.5%[4].

The course of the disease in the adolescent population is variable. Some adolescents with schizophrenia experience only one cycle of these phases, although most have multiple cycles[5]. The long-term outcome of adolescents diagnosed with schizophrenia has been studied by several investigators and psychiatrists in follow-up studies. In the majority of cases schizophrenia turned out to be a chronic or relapsing disorder with only a minority of patients that were fully employed or were attending school full-time[6].

In a published retrospective study[7] , only 37% and 42% of patients had no symptoms and no findings after follow-up examinations at 5 years and 11 years, respectively. Moreover, 21% and 20% of the patients were hospitalized for the entire 6 months proceeding the follow-up examinations at 5 and 11 years, respectively.

In this type II variation, the MAH applied for an extension of indication of Abilify as follows (the new indication is underlined):

'treatment of schizophrenia in adults and <u>in adolescents (13-17 years).'</u>

In addition, the MAH took the opportunity to update the details of the local representatives for Estonia, Belgium and Luxembourg.

2. Non Clinical aspects

Toxicology

To support the proposed extension of indication in adolescents (13-17 years), 4 non clinical studies were conducted to investigate the oral toxicity of aripiprazole in juvenile dogs (DM4042 and DM04023) and postnatal and/or juvenile rats (DN04081 and DN04048). The non clinical studies D04048 and DM4023 were not conducted in accordance with Good Laboratory Practices (GLP) as stated by the MAH.

In study DN04048, results suggested that rat exposure to aripiprazole and its metabolite was higher at earlier age (Post-Natal-Day or PND 7) and decreased with age. The values collected at the same PNDs were similar, reinforcing the idea that exposure change seen along time may be related to developmental aspects.

[1] Remschmidt & Theisen, 2005
[2] Burd & Kerbeshian, 1987
[3] Remschmidt et al., 1994
[4] Gillberg et al. , 1986
[5] McClellan et al. 1993, Werry et al. 1991
[6] Werry et al. 1991, Tsai & Champine 2004
[7] Krausz & Muller-Thomsen,1993

In study DN04081, oral administration of doses of 10, 20, and 40 mg/kg/day of aripiprazole to juvenile rats from PND 21-80 resulted in in-life, behavioral, developmental, and clinical and anatomic pathology findings. All drug-related findings in male rats and most findings in female rats were reversible. Additionally, no evidence of neurotoxicity was observed further to the microscopic examination of the brain finding in the study (i.e increased diagonal length across the striatum (caudate-putamen) of the brain in females) and this finding did not appear to translate into behavioural changes up to animal adulthood.

In study DM04042, the principal drug-related findings in juvenile dogs given daily doses of 3, 10, and/or 30 mg/kg aripiprazole for 6 months were pharmacologically mediated, central nervous system-related clinical observations (ie, hypoactivity, tremors, ataxia) in both sexes and minimally to mildly reduced body weight gain in females. There were no drug-related findings in the neurobehavioral assessment or in the comprehensive microscopic examination of the central and peripheral nervous systems at doses up to 30 mg/kg/day (systemic exposures up to 23100 ng.h/mL aripiprazole and 19100 ng.h/mL metabolite). All drug-related changes observed were reversible.

Environmental risk assessment (ERA)

At the time of the submission of this application, the MAH referred to the ERA previously submitted within the approved type II variation to extend the indication of oral aripiprazole in the treatment and prevention of manic episodes in Bipolar I disorder (EMEA/H/C/471/II/39).

Results of a number of ERA studies (OECD 106, OECD 211, OECD 308 and OECD 210) were subsequently evaluated by the CHMP as part of commitments and considered fulfilled, provided an updated ERA assessment was provided by the MAH.

During the assessment of this variation, the MAH provided further ERA update with currently available data on ecotoxicity and fate, which included new data on the Collembola Reproduction test ISO 11267. Following this update, the PEC/PNECsoil ratio changed from 0.0051 to 0.12.
Although the value of the PEC/PNEC soil ratio (<1), the CHMP considered that the terrestrial fate and effect analyses should be completed prior any conclusions are made on the terrestrial impact of aripiprazole. The MAH proposed to submit these studies, OECD 216 (Soil Micro-organism: Nitrogen Transformation Test) and 307 (Aerobic and anaerobic transformation in soil), and the updated ERA terrestrial compartment, as part of a follow-up measure, which was considered acceptable by the CHMP with an agreed deadline.

At present, the MAH predicted that the approval of oral aripiprazole in the new proposed indication will not significantly increase the use of aripiprazole in the EU. Based on available forecasts, the use of aripiprazole is estimated to account for approximately 1.0% of the total aripiprazole use in the EU.

Discussion on non clinical aspects

A comparative analysis of the findings observed in juvenile and adults animal studies was performed by the MAH. Results indicated that most of the effects observed in the juvenile rats, through administration in the two development periods were also observed in adults, many of these effects being possibly related to the pharmacological activity of aripiprazole.

Overall, the CHMP considers that the studies in juvenile animals did not give evidence for a different toxicological profile of aripiprazole in relation to adult animals, and did not raise particular developmental concerns regarding its use in paediatric patients ≥ 13 years of age as claimed in the proposed indication.

The main concerns related to potential effects of aripiprazole in postnatal development, including brain and sexual development, were covered during the treatment period in these non-clinical juvenile toxicity studies. Moreover, despite the fact that adult monkeys have been used to support the adult indication, the CHMP acknowledged the difficulties associated with the availability of the monkey

species and the handling aspects of very young animals, which justified the use of juvenile dogs as the non-rodent species.

According to the CHMP guideline on '*the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications'*(EMEA/CHMP/SWP/169215/2005, January 2008), appropriate studies in one species only could have been acceptable.

Considering that the systemic exposures of the animals at 40mg/Kg/day dose were 1.9-2.9 fold the exposures achieved in children with the dose of 30mg, the CHMP was of the opinion that these exposures were appropriate and in line with the recommendations provided in the above CHMP guideline.

The studies in juvenile animals did not give evidence for a different toxicological profile of aripiprazole in relation to adult animals, and did not raise particular developmental concerns regarding its use in pediatric patients ≥ 13 years of age as claimed in this application.

With respect to the ERA, the CHMP requested the MAH to provide a justification on the change of the Csludge value applied in the latest submitted ERA. Furthermore, a full ERA should be submitted once the terrestrial risk analysis is completed.

3. Clinical aspects

The clinical development program completed to support the proposed extension of indication in adolescents (13-17 years), consisted of:

- two Phase I studies to investigate the pharmacokinetic profile of aripiprazole in children and adolescent patients with a primary schizophrenia spectrum diagnosis, bipolar spectrum diagnosis, or other paediatric psychiatric disorders between the age of 10 - 17 years (Study **31-03-238**) and in children and adolescents with conduct disorders between the age of 6 - 17 years (Study **CN138014**);

- One randomised, double- blind, placebo controlled study (**31-03-239)**, conducted in adolescents (13 to 17 years), with a DSM-IV (Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition) diagnosis of schizophrenia, to assess the efficacy and safety of aripiprazole (two fixed doses, 10 mg and 30 mg) compared to placebo;

- Two phase III/IIIb open-label studies (**31-03-241 and 31-05-243**), designed to provide additional long term safety data of aripiprazole in the paediatric population. Patients who had completed study 31-03-239 were offered to continue in the open-label, flexible-dose study 31-03-241 for an additional 26 weeks; thereafter, patients who had completed study 31-03-241 were offered to continue in the open-label, flexible-dose study 31-05-243 (ongoing roll-over study).

Additional pharmacokinetic analysis **(study 31-05-242)** was performed and included a comparison with historical data from adults.

Pharmacokinetics

- **Dose proportionality and time dependencies**

1) <u>Study 31-03-238</u>

The objectives of the study were to evaluate the safety, tolerability and pharmacokinetics of repeated doses of aripiprazole following oral administration to children and adolescent subjects(10-17 years) with a primary diagnosis of schizophrenia or bipolar spectrum disorders. This was a multicenter, open-label, sequential cohort, dose-escalation trial with aripiprazole at doses ranging from 2 to 30 mg.

Subjects were treated in sequential cohorts receiving escalating doses of aripiprazole ranging from 2 mg to a maximum of 30 mg. After subjects were deemed eligible to participate, they entered the dose-escalation phase of the study. Subjects were administered aripiprazole oral tablets for a maximum of 12 days (depending of the maximum dose of the cohort) using a forced titration scheme to achieve one of the following dose levels: 20 mg, 25 mg, or 30 mg. Subjects then entered a fixed-dose phase and were administered the maximum dose for that cohort for 14 days.

A total of 21 subjects were enrolled, 8 subjects in the 20 mg cohort, 7 subjects in the 25 mg cohort, and 6 subjects in the 30 mg cohort. Seventeen subjects (81%) completed the dose-escalation and fixed-dose phases. Four subjects (19%) discontinued prematurely from the study, 2 (2/8; 25%) in the aripiprazole 20 mg cohort due to protocol deviation (n=1) and withdrawal of consent (n=1), and 2 (2/7; 29%) in the aripiprazole 25 mg cohort due to the AEs 'dystonic reaction' (n=1) and 'akathisia' (n=1), respectively.

Aripiprazole doses were titrated to the final fixed dose that was given for 14 days to achieve steady-state plasma concentrations. Mean plasma levels of aripiprazole peaked approximately 2 hours after the dose and declined slowly thereafter.

In children and adolescent subjects with different psychiatric diagnoses aged from 10 to 17 years the pharmacokinetics of aripiprazole were linear. C_{max} values were higher compared to adult subjects, due to differences in body weights. Oral clearance of aripiprazole was similar in children/adolescents and adults when adjusted for body weights. The AUC_{τ} ratio in children and adolescents was similar to that from adult subjects.

Similarly to aripiprazole, the pharmacokinetics of dehydro-aripiprazole (major active metabolite) were linear, and C_{max} values in children and adolescents were higher compared to adults because of lower body weights. The AUC_{τ} ratio of dehydro-aripiprazole relative to aripiprazole was similar between children/adolescents and adults.

2) *Study CN138014*

The objectives of this study were to assess the pharmacokinetics and safety of aripiprazole following multiple oral doses of approximately 0.1 mg/kg per day in children (6 to 12 years) and adolescents (13 to 17 years) with a diagnosis of conduct disorders. This was an open-label, 15-day, 3-center study with an optional 36-month open-label safety extension.

For Phase A (from Screening to Day 15), subjects received daily doses of approximately 0.1 mg/kg aripiprazole starting on Day 1 and continuing through Day 14. Specifically, administered daily doses were 1 mg for subjects weighing less than 25 kg, 2 mg for subjects weighing 25 to 50 kg, 5 mg for subjects weighing 50 to 70 kg, and 10 mg for subjects weighing more than 70 kg. If doses of 2 to 10 mg aripiprazole were poorly tolerated, subsequent doses may have been reduced at the Investigator's discretion. Subjects who successfully completed Phase A of the study were permitted to enter the 36-month extension period (Phase B) with no interruption of dosing.

A total of 23 subjects (12 children and 11 adolescents) were enrolled in the study. All subjects completed Phase A of the study and continued on into Phase B. During this phase, 5 subjects (21.7%) completed treatment.

Eighteen subjects (78.3%) were discontinued from the study. Of these, 7 subjects were lost to follow-up, 6 subjects were discontinued for non-compliance, 3 subjects withdrew consent, and 2 subjects discontinued for lack of efficacy and protocol dose limitations, respectively. No subjects were discontinued due to AEs. Ten subjects discontinued prior to completion of 1 year of the study (one subject discontinued prior to completion of Period A), 5 subjects discontinued after enrollment for between 1 and 2 years and 2 subjects discontinued after enrollment for over 2 years.

In children and adolescents who received a daily dose of aripiprazole through Days 1 to 14 of the study, aripiprazole geometric mean C_{max} and AUC values were between 2.4 and 6.4-times higher on Day 14 compared to Day 1. This extent of accumulation was similar for children and adolescents and was also similar to a 3- to 5-fold accumulation observed in young adults.

The apparent clearance values for aripiprazole were similar in children, adolescents, and adults when normalized for body weights, and appeared to be independent of the aripiprazole dose.

Steady-state was attained within 14 days of dosing in both paediatric and adult populations.

The overall metabolic profile was similar in children and adolescents. Similarly to adults, dehydro-aripiprazole was the predominant circulating metabolite in the plasma of children and adolescents with mean exposure values being approximately one-quarter to one-third of those of aripiprazole.

- **Additional pharmacokinetic analysis**

3) Study 31-05-242

The objectives of this study were to: 1) describe the pharmacokinetics of aripiprazole in children and adolescent patients (ages 10-17 years), 2) investigate the impact of key covariates, especially size and age, on the pharmacokinetics of aripiprazole and 3) estimate the between and random residual variability

The pharmacokinetic analysis contained 1,444 plasma samples of 343 patients from three different clinical studies (31-03-238, 31-03-239 and 31-03-240).

The demographics and size were relatively well-balanced across the three studies. Patient body weight correlates with age i.e from 10 to 14 years.

Typical population PK parameters (95% CI) given the reference covariates (70 kg weight and 50 kg lean body mass) were 3.44 (3.26, 3.63) L/h, 255 (231, 283) L, and 1.67 (0.748, 4.28) h^{-1} for CL, V, and Ka, respectively. Model performance assessments showed adequate precision of the parameter estimates and slight under prediction for concentrations greater than 650 ng/mL.

Approximately 3% of the concentrations were greater than 650 ng/mL.

The pharmacokinetic profile of aripiprazole in the paediatric patients was linear across evaluated doses.

The pharmacokinetic profile of aripiprazole in the analysed paediatric population appeared to be similar to adults, when compared to historical adult population pharmacokinetic analysis.

- **Discussion on pharmacokinetic aspects**

Based on studies 31-03-238 and CN138014, the linearity of the pharmacokinetic parameters of aripiprazole in children and adolescents can be considered as established. In the paediatric population, C_{max} levels were generally higher compared to those reported from studies with adults. However, when values were normalized for body weight, apparent oral clearance was similar in children, adolescents, and adults.

The CHMP noted that steady-state was attained after 14 days of oral daily (QD) dosing of aripiprazole; similarily to the time to steady-state observed in studies with adults. Aripiprazole accumulation after 14 days of dosing was similar between children and adolescents i.e 2.4- to 6.4-fold and adults i.e 3 to 5 fold.

The overall metabolic profile following oral dosing of aripiprazole was similar in children and adolescents, with dehydro-aripiprazole as the predominant circulating metabolite.

Clinical efficacy

- **Main clinical study**

1) Study 31-03-239

METHODS

Study design

This was a multicenter, randomized, double-blind, placebo-controlled trial.

Objective

The objective is to assess the safety and efficacy of two fixed doses of aripiprazole (10 mg and 30 mg) compared to placebo in adolescent subjects, 13 to 17 years of age (inclusive), with a DSM-IV diagnosis of schizophrenia.

Treatment period

After a minimum 3-day antipsychotic washout period, patients were evenly randomized to receive a double-blind medication as follows:

- Arm 1 (10 mg treatment arm): aripiprazole 2 mg QD for 2 days, aripiprazole 5 mg QD for 2 days, and aripiprazole 10 mg QD as the target dose, starting on Day 5;
- Arm 2 (30 mg treatment arm): aripiprazole 2 mg QD for 2 days, aripiprazole 5 mg QD for 2 days, aripiprazole 10 mg QD for 2 days, aripiprazole 15 mg QD for 2 days, aripiprazole 20 mg QD for 2 days, and aripiprazole 30 mg QD as the target dose, starting on Day 11;
- Arm 3 (placebo arm): matching placebo for aripiprazole tablets.

Aripiprazole was titrated to the target dose in 5 days in the 10 mg treatment arm and in 11 days in the 30 mg treatment arm. Subjects remained at the assigned dose for at least 2 weeks. Subjects who experienced dose-related tolerability issues prior to study Day 25 were to be discontinued from the study. Beginning on Day 26, investigators could decrease the dose of aripiprazole for tolerability (to 5 mg QD in the 10 mg treatment arm and to 15 mg QD in the 30 mg treatment arm).

Inclusion Criteria

Male and female subjects, 13 to 17 years of age, with a K-SADS-PL (Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime Version) confirmed Axis I (DSM-IV) diagnosis of schizophrenia. The initial diagnosis was to be made by an experienced clinician who was trained in treating adolescent patients with a psychiatric disorder. The DSM-IV diagnosis was confirmed by a K-SADS-PL interview administered by a trained clinician. Patients were to have a PANSS (Positive and Negative Syndrome Scale) Total Score ≥ 70 at baseline (Day 1).

Sample size

The study was designed to have 85% power given a difference between aripiprazole and placebo of -11.4 for the change from baseline in PANSS Total Score. The difference of -11.4 was the median of the mean differences seen in the adults for schizophrenia over the aripiprazole dose ranges of 2 to 10 mg QD and 2 to 30 mg QD. A pooled standard deviation (SD) of 22.5 was used.

Primary efficacy endpoint

The primary efficacy measure was the mean change from Baseline to Endpoint (Day 42) in the PANSS Total Score.

Secondary efficacy endpoints

Secondary efficacy measures were the mean changes in scores from Baseline to Endpoint (Day 42) in the Children's Global Assessment Scale (CGAS), Clinical Global Impression (CGI)-Severity Scale, CGI-Improvement Scale, and PANSS Positive and PANSS Negative Subscales; and time to discontinuation due to all reasons.

Other outcome measures

Other outcome measures were the mean changes from baseline to Endpoint (Day 42) in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) Total Score and Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) Overall Score.

Post hoc analyses

Post-hoc analyses were performed to determine the percentage of subjects achieving remission, defined as a score of mild or less (≤ 3) for items P1, P2, P3, N1, N4, N6, G5, and G9 in the PANSS Score.

RESULTS

Patient distribution

A total of 302 subjects were randomized and treated in this study: 100/302 (33.1%) in the aripiprazole 10 mg arm, 102/302 (33.8%) in the aripiprazole 30 mg arm, and 100/302 (33.1%) in the placebo arm. Of the 302 subjects randomized, all were analyzed for efficacy. All subjects having a baseline and a post-baseline efficacy measurement were included in a "change from baseline" analysis, and all subjects having a post-baseline measurement were included in CGI-I analysis based only on post-baseline measurements.

A total of 258/302 (85.4%) subjects completed the study (at day 42): 84/100 (84.0%) in the aripiprazole 10 mg arm, 84/102 (82.4%) in the aripiprazole 30 mg arm, and 90/100 (90.0%) in the placebo arm. Overall, AEs and subject withdrawal of consent were the most common reasons for discontinuation.
The mean age in the groups of patients treated with aripiprazole (10, 30 mg) or placebo was 15.6, 15.4, or 15.4 years, respectively, with a range between 13 and 17 years for each treatment group.

Baseline Psychiatric Characteristics

Baseline disease severity as determined by PANSS Total Score and Children's Depression Rating Scale – Revised (CDRS-R) Suicidal Ideations Score are summarised in Table 1.

Table 1: Baseline Disease Severity

Baseline Characteristics	Statistic	Aripiprazole 10 mg (N = 100)	Aripiprazole 30 mg (N = 102)	Placebo (N = 100)	Total (N = 302)
PANSS Total Score	N Mean (SD)	100 93.6 (15.7)	102 94.0 (16.1)	100 94.6 (15.6)	302 94.1 (15.8)
CDRS-R Suicidal Ideation Score	N Mean (SD)	100 1.3 (0.6)	102 1.3 (0.6)	99 1.3 (0.5)	301 1.3 (0.6)

Furthermore, a total of 67.5% of all patients included in this study used baseline medications prior to the start of the study. Psycholeptics were used by a total of 59.6% of patients.

Extent of Exposure

The average daily dose overall during the study was 8.9 mg in the aripiprazole 10 mg arm and 22.5 mg in the aripiprazole 30 mg arm.

Primary efficacy endpoint

The mean change from baseline in PANSS Total Score at Week 6 is presented in Table 2 for the Last Observation Carried out Forward (LOCF) data set.

Table 2 PANSS Total score: mean change from baseline to week 6 (LOCF)

Treatment group	Baseline[a]		Week 6		Difference in mean change vs placebo	95% Confidence interval	p-value[c]
	N	LS Mean[b]	N	LS Mean			
Placebo	98	95.0	98	-21.2	-	-	
Aripiprazole 10 mg	99	93.7	99	-26.7	-5.46	-10.7 − -0.21	0.0414
Aripiprazole 30 mg	97	94.9	97	-28.6	-7.40	-12.7 − -2.13	0.0061

[a] For baseline, N and Mean are provided. Maximum positive score = 210.

[b] LS mean differences are derived from an ANCOVA model of change from baseline with baseline as a covariate and terms for treatment and region strata. A negative LS mean difference indicates improvement.

[c] The p-values were derived from Student's t-tests on estimate of treatment comparisons, which were based on least square means

Aripiprazole 10 mg and 30 mg showed statistically significant improvements over placebo in the PANSS Total Score at Week 6.
Using the LOCF data set, the PANSS Total Scores at Week 6 were -26.7 in the aripiprazole 10 mg arm, -28.6 in the aripiprazole 30 mg arm, and -21.2 in the placebo arm.

The comparison between aripiprazole and placebo was significant at both doses ($p = 0.0414$ for ariprazole 10 mg versus placebo and $p = 0.0061$ for aripiprazole 30 mg versus placebo). The difference from placebo in mean change from baseline at Week 6 was −5.46 (95% CI = -10.7 to -0.21) for the aripiprazole 10 mg arm and -7.40 (95% CI = -12.7 to -2.13) for the aripiprazole 30 mg arm.

Secondary efficacy endpoints

Positive and Negative Syndrome Scale PANSS Total Score at all Visits Other Than Week 6

The aripiprazole 10 mg arm showed improvements over the placebo arm in the change from baseline in PANSS Total Score at all visits; however, the improvements were only statistically significant compared with placebo at Week 6. The aripiprazole 30 mg arm showed statistically significant improvements over placebo in the change from baseline in PANSS Total Score at Week 1 (-10.4

versus -7.2 (p = 0.0465), Week 3 (-22.1 versus -16.7, p = 0.0269), Week 4 (-24.6 versus -19.0, p = 0.0181), and Week 5 (-27.3 versus -20.3, p = 0.0057).

Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Positive Subscale Score

The aripiprazole 10 mg arm showed statistically significant improvements over the placebo arm at Week 5 (-7.2 versus -5.6, p = 0.0276) and Week 6 (-7.6 versus -5.6, p = 0.0134). The difference from placebo in mean change from baseline at Week 6 was -1.95 (95% CI = -3.49 to -0.41; p = 0.0134) for the aripiprazole 10 mg arm.

The aripiprazole 30 mg arm showed statistically significant improvements over placebo at Week 1 (-2.9 versus -1.8, p = 0.0256), Week 3 (-6.2 versus -4.6, p = 0.0270), Week 4 (-7.1 versus -5.3, p = 0.0118), Week 5 (-7.8 versus -5.6, p = 0.0029), and Week 6 (-8.1 versus -5.6, p = 0.0018) (LOCF). The difference from placebo in mean change from baseline at Week 6 was -2.47 (95% CI = -4.02 to -0.92; p = 0.0018) for the aripiprazole 30 mg arm.

Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Negative Subscale Score

The aripiprazole 10 mg arm showed statistically significant improvements over the placebo arm in the mean change from baseline in PANSS Negative Subscale Score at Week 6 (-6.9 versus -5.4, p = 0.0462). The difference from placebo in mean change from baseline at Week 6 was -1.55 (95% CI = -3.07 to -0.03; p = 0.0462) for the aripiprazole 10 mg arm.

The aripiprazole 30 mg arm showed statistically significant improvements over placebo at Week 3 (-5.4 versus -4.0, p = 0.0410) and Week 4 (-6.0 versus -4.6, p = 0.0427). The difference from placebo in mean change from baseline at Week 6 was -1.29 (95% CI = -2.82 to 0.24; p = 0.0972) for the aripiprazole 30 mg arm.

Change From Baseline in Children's Global Assessment Scale (CGAS) Score

Both the aripiprazole 10 mg and 30 mg arms showed statistically significant improvements over the placebo arm in the change from baseline in CGAS Score. At Week 6, the mean changes from baseline using LOCF were 14.7, 14.8, and 9.8 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively (p = 0.0054 for 10 mg versus placebo and p = 0.0044 for 30 mg versus placebo). The difference from placebo in mean change from baseline at Week 6 was 4.93 (95% CI = 1.47 to 8.39; p = 0.0054) for the aripiprazole 10 mg arm and 5.08 (95% CI = 1.60 to 8.57; p = 0.0044) for the aripiprazole 30 mg arm.

Change From Baseline in Clinical Global Impression (CGI) Severity Score

The aripiprazole 10 mg arm showed statistically significant improvements over the placebo arm at Week 3 (-0.8 versus -0.6, p = 0.0399), Week 5 (-1.1 versus -0.8, p = 0.0252), and Week 6 (-1.2 versus -0.9, p = 0.0071). The difference from placebo in mean change from baseline at Week 6 for the aripiprazole 10 mg arm was -0.36 (95% CI = -0.62 to -0.10; p = 0.0071).
The aripiprazole 30 mg arm showed statistically significant improvements over placebo at Week 1 (-0.3 versus -0.2, p = 0.0210), Week 3 (-0.9 versus -0.6, p = 0.0023), Week 4 (-1.0 versus -0.8, p = 0.0158), Week 5 (-1.1 versus -0.8, p = 0.0031), and Week 6 (-1.3 versus -0.9, p = 0.0016) (LOCF). The difference from placebo in mean change from baseline at Week 6 for the aripiprazole 30 mg arm was -0.42 (95% CI = -0.68 to -0.16; p = 0.0016).

Clinical Global Impression (CGI) Improvement Score

The aripiprazole 10 mg arm showed statistically significant improvements over the placebo arm at Week 1 (3.6 versus 3.8, p = 0.0175), Week 5 (2.8 versus 3.2, p = 0.0239), and Week 6 (2.7 versus 3.1, p = 0.0167). The difference from placebo in mean change from baseline at Week 6 was -0.45 (95% CI = -0.82 to -0.08; p = 0.0167) for the aripiprazole 10 mg arm.

The aripiprazole 30 mg arm showed statistically significant early onset of improvements over placebo at Week 1 (3.4 versus 3.8, p = 0.0013), Week 3 (2.8 versus 3.2, p = 0.0044), Week 4 (2.7 versus 3.2, p = 0.0033), Week 5 (2.6 versus 3.2, p = 0.0002), and Week 6 (2.5 versus 3.1, p = 0.0004). The difference from placebo in mean change from baseline at Week 6 was -0.61 (95% CI = -0.94 to -0.28; p = 0.0004) for the aripiprazole 30 mg arm.

Other Outcome Measures

Change From Baseline in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) Total Score

Using the LOCF data set, improvements were observed in all three treatment arms; however, no statistically significant differences were observed between either of the aripiprazole arms and placebo.

Change From Baseline in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) Overall Score

Using this data set, baseline scores were statistically significantly higher in the placebo arm than in the aripiprazole 10 mg arm (p = 0.0477). At Week 6, statistically significant improvements compared to placebo were seen in the aripiprazole 10 mg arm (0.6 versus 0.1, p = 0.0045) and the aripiprazole 30 mg arm (0.6 versus 0.1, p = 0.0030). The difference from placebo in mean change from baseline at Week 6 was 0.41 (95% CI = 0.13 to 0.68; p = 0.0045) for the aripiprazole 10 mg arm and 0.40 (95% CI = 0.14 to 0.67; p = 0.0030).

Post hoc analysis - Percentage of Subjects Achieving Remission

Using the LOCF data set, the percentage of subjects achieving remission was statistically significantly greater than placebo for the 10 mg aripiprazole arm (53/99, 53.5% for aripiprazole 10 mg compared with 35/98, 35.7% for placebo; p = 0.0130); as well as for the 30 mg aripiprazole arm (56/97, 57.7%; p = 0.0024 against placebo).

- **Supportive studies**

1) *Study 31-03-241*

METHODS

Study design

This was a multicenter, open-label, flexible dose study. All subjects enrolled in Study 31-03-241 had previously completed Study 31-03-239 (adolescents with schizophrenia) or had withdrawn from the double-blind extension phase of Study 31-03-240 (children and adolescents with bipolar I disorder).

Subjects enrolled in Study 31-03-241 were eligible to receive up to a total of 6 months of open-label aripiprazole treatment at daily doses of 2 mg to 30 mg. The open-label trial overlapped with the parent study for 1 day. The End of Treatment evaluations conducted at the last office visit of the parent study served as baseline (Day 0) evaluation for this open-label trial.

Objective

The objective is to assess the long-term safety and tolerability of aripiprazole by enrolling subjects from the parent studies.

Statistical methods

Efficacy and other outcome measures were summarised as changes from baseline using descriptive statistics.

Efficacy outcome measures

The efficacy outcome measures for subject with schizophrenia were mean changes from baseline on the Positive and Negative Syndrome Scale (PANSS) Total Score, the Positive and Negative subscales; the Clinical Global Impression Severity Scale (CGI-S) score and mean CGI-I score; the Children's Depression Rating Scale-Revised (CDRS-R); the Children's Global Assessment Scale (CGAS); evaluated by visit.

Other outcome measures

The Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) (translated into different languages when applicable) was completed by each subject at baseline (Day 0) and End of Treatment/Early Termination (Week 26).

RESULTS

Patient distribution, Extent of Exposure

A total of 239 adolescent schizophrenia patients from the parent study 31-03-239 were enrolled, for whom an average daily dose of aripiprazole of 16.7 mg was calculated. One hundred and eighty-one subjects (75.7%) completed the study. A total of 28/239 (11.7%) subjects withdrew consent and 7/239 (2.9%) were lost to follow-up. 6/239 (2.5%) subjects discontinued study medication due to AEs.

For two of the patients, no post-baseline measurement for any efficacy endpoint was available. Of the remaining 237 patients, for whom efficacy results were available, 80 patients were treated with 10 mg aripiprazole, 78 patients with 30 mg aripiprazole and 79 patients were treated with placebo in the parent study.

Primary efficacy measures

PANSS Total Score

During this study, improvements were observed at each post-baseline visit. The greatest improvement was observed in the subjects formerly in the placebo arm of the parent study, who showed a mean decrease from baseline in PANSS Total Score of -10.71 at the Last Visit. For subjects formerly in the 10 mg and 30 mg aripiprazole treatment arms, improvements were maintained over time, including at the Last Visit (mean changes from baseline of -5.23 and -6.21, respectively).

CGI Severity Score

During this study, improvements were observed at each post-baseline visit starting at Week 2 for the total aripiprazole group. The greatest improvement seen at Last Visit was in the subjects formerly in the placebo arm of the parent study, who showed a mean decrease from baseline in CGI-S of -0.70. For subjects formerly in the aripiprazole 10 mg and 30 mg treatment groups, improvements were maintained over time starting from Weeks 2 to 3, including at the Last Visit (mean changes from baseline of -0.38 and -0.45, respectively).

CGI Improvement Score

For the CGI-Improvement, a lesser mean score indicated improvement. At Week 1, the mean scores in the groups that formerly received aripiprazole 10 mg, aripiprazole 30 mg, and placebo, respectively, were 2.82, 3.06, and 3.14, which generally indicated improvement. Scores were decreased from these Week 1 values for all three groups at every subsequent visit, indicating improvements at each visit over time. The greatest improvement seen at the Last Visit was in the subjects formerly in the aripiprazole 30 mg arm of the parent study, who had a mean CGI-I Score of 2.38 at the Last Visit compared to 3.06 at Week 1. For subjects formerly in the 10 mg and placebo treatment arms, improvements were also observed at the Last Visit, with mean scores of 2.26 and 2.53 compared with Week 1 scores of 2.82 and 3.14, respectively.

PANSS Positive Subscale Score

During this study, improvements were observed at each post-baseline visit. The greatest improvement seen was in the subjects formerly in the placebo arm of the parent study, who showed a mean decrease from baseline in PANSS Total Score of -2.91 at the Last Visit. For subjects formerly in the 10 mg and 30 mg treatment arms, improvements were maintained over time; at the Last Visit, the mean changes from baseline were -1.61 and -1.87, respectively.

PANSS Negative Subscale Score

During this study, improvements were observed at each post-baseline visit. The greatest improvement seen was in the subjects formerly in the placebo arm of the parent study, who showed a mean decrease from baseline in PANSS Total Score of -3.03 at the Last Visit. For subjects formerly in the 10 mg and 30 mg treatment arms, improvements were maintained over time; at the Last Visit, the mean changes from baseline were -1.33 and -1.70, respectively.

Children's Global Assessment Scale Score

The greatest improvement seen was in the subjects formerly in the placebo arm of the parent study, who showed a mean increase from baseline in CGAS Score of 8.90 at the Last Visit. For subjects formerly in the 10 mg and 30 mg treatment arms, improvements were maintained over time; at the Last Visit, the mean changes from baseline were 6.86 and 6.97, respectively.

Children's Depression Rating Scale – Revised Score

The greatest improvement seen was in the subjects formerly in the placebo arm of the parent study, who showed a mean decrease from baseline in CDRS-R Score of -5.49 at the Last Visit. For subjects formerly in the 10 mg and 30 mg treatment arms, improvements were maintained over time; at the Last Visit, the mean changes from baseline were -1.62 and -2.83, respectively.

Other outcome measures

Change From Baseline in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) Total Score

The greatest improvement seen was in the subjects formerly in the placebo arm of the parent study who showed a mean increase from baseline in P-QLES-Q Total Score of 2.28 at the Last Visit. For subjects formerly in the 10 mg and 30 mg treatment arms, improvements were maintained over time (mean change from baseline 0.67 and 0.57, respectively).

Change From Baseline in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) Overall Score

The greatest improvement seen was in the subjects formerly in the placebo arm of the parent study, who showed a mean increase from baseline in P-QLES-Q Overall Score of 0.16 at the Last Visit. For subjects formerly in the 10 mg and 30 mg treatment arms, test scores were slightly decreased at the Last Visit (mean changes from baseline of -0.01 and -0.08, respectively).

1) *Study 31-05-243 (ongoing)*

This study is currently ongoing. An interim analysis was conducted with a cut-off date of 21 June 2007.

METHODS

Study design

This is an open-label multicenter, rollover study.

Objective

The objective is to continue to provide flexible doses of aripiprazole therapy (5 mg, 10 mg, and/or 15 mg tablets) to adolescents (13-17 years of age) and adults (adolescents who reached 18 during the studies 31-03-239 or 31-03-241) male and female subjects with a DSM-IV diagnosis of schizophrenia and who had completed the study 31-03-241 for patients from countries in which aripiprazole is currently unavailable through marketed means.

Treatment period

Each subject received daily aripiprazole at a dose between 5 and 30 mg established in the study 31-03-241. However, modifications to the daily dose could be made at the investigator's discretion, if clinically warranted.

Following the Baseline visit, there are four study visits during the first year of treatment, three visits during the second year, and twice a year thereafter.

Statistical Methods

Efficacy and other outcome measures were summarised as changes from baseline using descriptive statistics.

Efficacy Outcome Measures

A Clinical Global Impression-Severity (CGI-S) Scale is collected to assess the continuation of therapeutic benefit of the aripiprazole treatment for the adolescent subject. The CGI-S score is summarized over time.

The Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) is administered in translated languages when available.

RESULTS

Patient distribution

As of this date, a total of 85 patients have been included in this study. Of 85 subjects included, 10 (11.8%) discontinued the study prematurely and the remaining 75 (88.2%) are ongoing. Among the

discontinuations, 4 (4.7%) withdrew for adverse events, 3 (3.5%) met withdrawal criteria (aripiprazole became commercially available for 2 subjects and one had a positive drug screen for cocaine), 2 (2.4%) withdrew consent, and 1 (1.2%) withdrew for lack of efficacy.
Clinical Global Impression - Severity (CGI-S)

Paired data for change from baseline in CGI-S were available for 82, 69, 26, and 3 subjects at Months 3, 6, 9, and 12, respectively . Mean scores for CGI-S ranged from 2.26 at Month 3 to 1.67 at Month 12. These values represented decreases from baseline at each timepoint evaluated (range −0.11 at Month 3 to −0.67 at Month 12), indicating maintenance of efficacy with aripiprazole treatment. The analysis at the last visit which included data from subjects who discontinued prematurely also showed maintenance of efficacy.

Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q)

Paired values for P-QLES-Q, a quality of life outcome that was assessed semi-annually, were available for 66 (total score) and 68 subjects (overall score) at Month 6, but only 3 subjects at Month 12. Summary data from the last scheduled visit which included ongoing and withdrawn subjects showed little change from baseline, indicating that efficacy was maintained for up to one year in this study. The overall rating of 3.82 on the P-QLES-Q indicated that on average the subjects' quality of life, enjoyment, and satisfaction were better than fair and approaching good at the last visit.

- **Discussion on clinical efficacy**

Results from study 31-03-239, a large randomised controlled trial conducted in adolescents, with a mean age around 15, showed that aripiprazole was effective in the treatment of schizophrenia in this target population at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared with placebo in the primary efficacy endpoint, PANSS Total Score at Week 6 (LOCF).

Aripiprazole 10 mg and 30 mg were effective at Week 6 in the treatment of schizophrenia in adolescents based on statistically significant improvements compared with placebo in secondary efficacy endpoints (LOCF) that included change from baseline in PANSS Positive Subscale Score, CGAS Score, and CGI-Severity Score, and mean CGI-Improvement Score.

However, the CHMP was concerned about the studied population which may not have reflected the characteristics of the European population, given that study 31-03-239 was performed in a number of non European countries. Following detailed analysis provided by the MAH on the characteristics of the studied population, the CHMP was particularly reassured that the percentage of previous antipsychotic medication in study 31-03-239 was similar to that observed in adolescent patients being treated in Europe for the same condition.

Furthermore, the CHMP raised a major concern related to the size of the treatment effect in comparison with that observed in the adult population. Also, data on remission rates were collected from a post-hoc analysis, which questioned the clinical relevance of these results.

To address these concerns, the MAH performed 2 comparative analyses of results according to original and post-hoc statistical analyses, respectively. The first analysis showed that the 95% confidence interval for the treatment difference between aripiprazole and placebo for the paediatric study (31-03-239) and adult study (CN-138-001) were overlapping. The range of the effect size was rather similar between these two populations. The 7 point (point estimate value) observed for the 30 mg dose arm in the adolescent Study 31-03-239 falls well within the 95% confidence intervals observed for the adult Study CN-138-001. The second analysis showed that the standardized difference for treatment differences from placebo (effect size) for mean change from baseline in PANSS Total score between the 30 mg aripiprazole and placebo groups in the paediatric population was similar to that of adults dosed at 10, 15, and 20 mg/day.

The MAH also emphasized that there is a clear trend of improvement over the time course of the adolescent trial confirming a positive drug effect for both 10 mg and 30 mg aripirazole doses. The treatment effect was consistent as shown by the steady progression of improvement observed in all outcome measures (PANSS total score, PANSS positive symptoms subscale and CGI Improvement score) as compared to placebo from Weeks 3-6. This was noted in both the 10 mg and 30 mg arms.

On the basis of the above and despite data on remission rates were collected as post-hoc analysis, the CHMP considered that overall, the short-term efficacy results could support the proposed paediatric indication.

With respect to the long-term data, only open label studies were performed. The lack of active comparator and the open label design make the results of the submitted extension studies difficult to interpret.

In light of these concerns, the CHMP requested the PDCO to discuss whether a study with long-term efficacy data for aripiprazole in the proposed indication would be required and the feasibility and value of a randomised controlled withdrawal trial in this setting. The main PDCO conclusions were the following:

- Efficacy and safety data for antipsychotics cannot safely be extrapolated between different age groups (adult versus. different paediatric subgroups) or between indications (e.g. schizophrenia and bipolar), as susceptibility to primary and secondary pharmacodynamic effects may be different across age groups and indications. Therefore, a 6 month maintenance study in adolescents with schizophrenia, and an 8 week duration efficacy study in adolescents to assess the effect of the treatment upon negative symptoms would be required. Long-term safety data would also be required

- Although schizophrenia is considerably rarer in adolescents than in adults, the PDCO considered that such studies are feasible.

Subsequently, the CHMP agreed to convene a Scientific Advisory Group (SAG) Central Nervous System (with additional experts in child psychiatry) to discuss in further details the need for long-term efficacy data for aripiprazole in the proposed paediatric indication. The SAG CNS was held on 5 February 2009 and the main conclusions were the following:

- In general terms continuity in the phenomenology of schizophrenia is recognised across ages. However the manifestations of disease are often more severe with a worst prognosis and disease appears less responsive to treatment in younger patients with respects to adults.

- Incidence of schizophrenia rises with age. No specific differences are observed across age *strata* except the very rare observation of cases in the youngest individuals; schizophrenia is also very rare during pre-puberty.

- The efficacy of antipsychotics on positive/negative symptoms is not different *per se,* nevertheless in relation with the greater severity of the syndrome more variability in the response is commonly observed in adolescents. Pharmacological benefits are not systematically different but less predictable in individual patients.

- Linear correlation in the pharmacokinetic parameters is not considered appropriate for extrapolation of efficacy, since possible differences exist in terms of dopaminergic receptors density in the brain of adolescents and children with respect to adults. Therefore the dosage regimen is not directly comparable in adolescents/children and adults.

- Ideally, a 6-12 month duration efficacy maintenance study versus active treatment (*best available used pharmacological treatment*) is also recommended to completing the data extrapolated from relapse prevention randomised clinical trials already performed in adults. Six months is seen as a minimum duration to effectively capture relapses (which are becoming frequent after 5.5 months), and results observed over 12-month duration would be more relevant.

Having considered the SAG conclusions, the available short-term efficacy results and further comparative analyses provided with the adult population (e.g in a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74% of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial and was similar to the long-term efficacy seen in adults), the CHMP considered that the extrapolation from the adult to the adolescent populations was still questionable, although it was expectable that the older adolescent group might be closer to the adult population.

Whereas:

- The overall database on schizophrenia in children and adolescents is limited compared to the adult population;
- There is clinical experience with several antipsychotics regarding pharmacological treatment options, however, there is no established gold standard yet,
- Poor responding to treatment resulting in worse outcome compared to adult patients, may make extrapolation of data of the adult population to adolescents and children difficult, particularly with regard to patients with first episode schizophrenia or symptoms not fulfilling the diagnostic criteria yet;

The CHMP also agreed to convene a follow up SAG to discuss in further details the clinical requirements for development of medicinal products for the treatment of schizophrenia in children and adolescents. The SAG was held on 11 May 2009 and the main conclusions were the following:

- Short-term trials (randomized, double-blind, placebo-controlled) are actually needed to prove efficacy and safety of antipsychotics in the younger population.

The recommended duration is 6-8 weeks. PANSS can be used to assess signs and symptoms of schizophrenia in the paediatric population whether it is recognised this tool is not validated before the age of 14 years. Other scales may equally be considered to assess specific dimensions (negative symptoms), if adequate validation is provided. Co-morbidities should not represent a systematic cause for exclusion.

For the time being considering the lack of definitive clinical evidences the use of an active control (instead of placebo) is not recommended.

- Phenomenology of schizophrenia is considered as a continuum, very rare in children (under 12 years), where it usually comes with a severe prognosis but steadily more frequent after puberty and in late adolescence where the clinical course becomes more similar to the young adults, without any recognizable age threshold.

- Maintenance of efficacy can not be extrapolated from clinical trials conducted in adults (often patients with chronic forms of schizophrenia are already in their 40s) to children and or adolescents (with a shorter course of disease, different physiologic status and possibly different susceptibility to safety risks).

There is noticeable lack of information on the natural course of the disease in the paediatric population. However the follow up SAG felt that a reasonable duration for maintenance studies is 12 months.

Definition of relapse in this population should be based on absolute increase of PANSS (possibly looking to the most specific items) rather than on relative worsening of total score. Superiority studies are not ruled out however the randomised withdrawal design versus placebo is the most informative methodology both in terms of maintenance of efficacy and for the evaluation of safety.

While the follow up SAG recognised the difficulties in implementing long-term maintenance studies versus placebo arm, nevertheless in the lack of long term safety data it is considered equally risky to expose the adolescents to a product approved for the adults (because of risks of endocrine unbalance

or weight gain, or Extra-Pyramidal Symptoms, or cognitive problems among others) and the safety risks of the new drug could be easily underestimated versus the ones of the "active control(s)".
The follow up SAG recommended both treatment groups receive background better standard of care (like *familial/behavioural therapy, cognitive rehabilitation programs*) over 12 months.

- The follow up SAG also considered that no golden standard is available (see also above) because of current lack of controlled clinical data in the paediatric population. Currently each child/adolescent psychiatry department mostly follows his own clinical practice largely guided by experience with antipsychotics build in other indications and on safety considerations applied to the individual case. Low ineffective dosages may be used. Switch to clozapine or augmentation strategies are also applied in variable extent according to centres and country.

During the oral explanation held on 20 July 2009, the MAH provided the following argumentation to support an indication in adolescents 15 years and older:

- To address the CHMP concerns over the influence of sexual maturation on disease progression and responsiveness to treatment in adolescent patients with schizophrenia, particularly at pre-pubertal and pubertal stages, the MAH presented data indicating similar acute and long-term efficacy results compared to adults,

- To address the validity of the extrapolation of long-term efficacy from adult data, adolescent patients (15-17 years, from study 31-03-239/241) were compared to a subgroup of adult patients with early episode of schizophrenia (from previous adult study 31-98-217/304), characterised by: age < 40 years and shorter duration of disease i.e. ≤ 5 years since first episode). Results showed similar baseline PANSS score of 95.0 and 93.4 for adults and adolescents, respectively and the percentage of patients with treatment response was comparable in these populations.

Having considered the follow up SAG conclusions and the oral explanation provided by the MAH, the CHMP considered the proposed indication approvable provided that in terms of efficacy:
- The paediatric population is restricted to adolescents older than 15 year-old;
- Long-term study to further support the maintenance of the effect is performed by the MAH, as part of a post-authorisation commitment.

In terms of the dosing recommendation, the MAH proposed to titrate aripiprazole with a starting dose of 2 mg to 5 mg after 2 days and to the target dose of 10 mg after two additional days. Subsequent dose increases should be administered in 5 mg increments. The maximum daily dose should not exceed 30 mg. The CHMP acknowledges that the 2 mg dose is only available with the oral solution (1mg/ml) formulation and considered the proposed dosing recommendation acceptable.

Clinical safety

- **Patient exposure**

The safety sample comprised a total of 303 adolescent subjects with schizophrenia who were enrolled in five studies (CN138014, 31-03-238, 31-03-239, 31-03-241 and 31-05-243). Of these, 282 subjects were exposed to aripiprazole.

In a pooled analysis from 3 phase III/IIIb studies (31-03-239,31-03-241 and 31-05-243), Seventy six subjects (27.0%) were exposed to aripiprazole for more than 52 weeks, and 3 subjects (1.1%) for more than 78 weeks.

- **Adverse events**

Study CN138014

A total of 132 AEs occurred; 48 in 17 (73.9%) subjects in Phase A, and 84 in 17 (73.9%) subjects in Phase B. All of the events were of mild to moderate intensity. Twenty-six TEAEs with no resolution

date occurred during the study (6 events in 6 subjects during Phase A and 20 events in 13 subjects during Phase B).

The AE profiles were generally similar in children and adolescents with most of the AEs occurring in the gastrointestinal disorders and nervous system disorders system organ classes.

There were 8 subjects (4 children and 4 adolescents) who experienced 11 marked laboratory abnormalities (MAs). One of these was reported as an AE. One child had an AE of increased hepatic enzymes reported. The subject had elevations in both ALAT and ASAT that were considered MAs. Other MAs included an additional subject with increased in ALAT, 3 subjects with decreased hemoglobin, 2 subjects with increased urinary glucose, and 1 subject each with increased alkaline phosphatase, uric acid and eosinophils.

Study 31-03-238

All 21 subjects enrolled reported at least one TEAE. The fewest number of TEAEs was reported in the Aripiprazole 30 mg cohort. No clear dose-related trends were observed.

One subject (aripiprazole 25 mg cohort) experienced a TEAE of acute dystonic reaction, considered by the investigator to be definitely related to aripiprazole.

Study 31-03-239

A total of 567 TEAEs were reported by 202/302 (66.9%) subjects (see Table 3). The percentage of subjects who experienced at least one TEAE was slightly higher in the aripiprazole arms than in the placebo arm. A total of 188 TEAEs were experienced by 71/100 (71.0%) subjects in the aripiprazole 10 mg arm; 232 TEAES were experienced by 74/102 (72.5%) subjects in the aripiprazole 30 mg arm; and 147 TEAEs were experienced by 57/100 (57.0%) subjects in the placebo arm.

The majority of TEAEs in all treatment arms were mild to moderate in severity. A greater percentage of subjects in the aripiprazole 10 mg arm experienced severe TEAEs (7/100, 7.0%) than did subjects in the aripiprazole 30 mg arm (4/102, 3.9%) or subjects in the placebo arm (3/100, 3.0%).

Table 3: Most Commonly Reported TEAEs by 5% or Greater Incidence

SOC and MedDRA Preferred Term	Aripiprazole 10 mg (N=100) n (%)	Aripiprazole 30 mg (N=102) n (%)	Placebo (N=100) n (%)	Total (N=302) n (%)
Total subjects with at least one TEAE	71 (71.0)	74 (72.5)	57 (57.0)	202 (66.9)
Gastrointestinal disorders				
Nausea	9 (9.0)	10 (9.8)	6 (6.0)	25 (8.3)
Vomiting	5 (5.0)	3 (2.9)	5 (5.0)	13 (4.3)
Infections and infestations				
Nasopharyngitis	5 (5.0)	5 (4.9)	4 (4.0)	14 (4.6)
Nervous system disorders				
Akathisia	5 (5.0)	12 (11.8)	5 (5.0)	22 (7.3)
Dizziness	7 (7.0)	4 (3.9)	3 (3.0)	14 (4.6)
Extrapyramidal disorder	13 (13.0)	22 (21.6)	5 (5.0)	40 (13.2)
Headache	16 (16.0)	11 (10.8)	10 (10.0)	37 (12.3)
Somnolence	11 (11.0)	22 (21.6)	6 (6.0)	39 (12.9)
Tremor	2 (2.0)	12 (11.8)	2 (2.0)	16 (5.3)

SOC and MedDRA Preferred Term	Aripiprazole 10 mg (N=100) n (%)	Aripiprazole 30 mg (N=102) n (%)	Placebo (N=100) n (%)	Total (N=302) n (%)
Psychiatric disorders				
Agitation	1 (1.0)	3 (2.9)	5 (5.0)	9 (3.0)
Insomnia	11 (11.0)	10 (9.8)	15 (15.0)	36 (11.9)

Note: Subjects were counted only once, per term, for the most severe of multiple occurrences of a specific MedDRA-preferred term

There appeared to be a general trend of increasing incidence across the treatment groups for TEAEs of nausea, akathisia, extrapyramidal disorder, somnolence, and tremor, with the highest incidence in the aripiprazole 30 mg arm.

There was 1 suicidal ideation event in the aripiprazole 30 mg arm (1%), and 1 suicidal attempt and 1 suicidal ideation (1% each) in the placebo arm.

An overall low incidence of clinically significant hyperprolactinemia was observed in this study: 3% in the aripiprazole 10mg arm, 0% in the aripiprazole 30 mg arm, and 6% in the placebo arm.

The incidences of low prolactin levels were 8%, 34%, and 26%, respectively, in the placebo, aripiprazole 10 mg, and aripiprazole 30 mg arms.

There was no signal of increased abdominal obesity associated with aripiprazole in this study.

No clinically meaningful changes were observed in the overall evaluation of metabolic parameters.

Study 31-03-241

A total of 499 TEAEs were experienced by 165/239 (69.0%) of the subpopulation of subjects with schizophrenia. The most common TEAEs reported at an incidence of ≥ 5% in the subpopulation of adolescents with schizophrenia were extrapyramidal disorder (19.2%), somnolence (13.8%), insomnia (9.2%), akathisia (8.4%), weight increased (7.9%), headache (7.1%), nausea (6.7%), tremor (6.3%), vomiting (5.9%), nasopharyngitis (5.9%), and increased appetite (5.4%).

Overall, EPS-related AEs were observed in 63/239 (26.3%) adolescent with schizophrenia.

Only 1 (0.3%) case of suicidal ideation was reported.
No clinically relevant transaminase elevations or changes in hematology parameters were noted in adolescents with schizophrenia.

No clinically meaningful changes in mean QT or QTc intervals, or other ECG abnormalities, were observed following long-term treatment with aripiprazole.

In adolescent subjects with schizophrenia, at the Last Visit, the percentage of subjects who experienced a potentially clinically significant weight gain (defined as ≥ 7% weight gain compared to baseline) was 24.5%; 4.6% of subjects experienced a weight loss of ≥ 7% relative to baseline.

Study 31-05-243

At least one TEAE was reported by 48.2% of subjects receiving long-term treatment with aripiprazole. The majority of TEAEs were mild or moderate in intensity.

The most common TEAEs (≥ 5% of subjects), irrespective of causality, were influenza (7.1%) and vomiting (5.9%). Extrapyramidal and akathisia events were reported by 5.8% and 2.3% of subjects, respectively.

No clinically meaningful changes in mean QTc intervals were evident in this sample population.

At the last visit, the percentage of subjects who experienced a potentially clinically significant weight gain (defined as ≥ 7% weight gain compared to baseline) was 12.7%; whereas, 7.0% of subjects experienced a weight loss of ≥ 7% relative to baseline.

There was no signal of increased abdominal obesity associated with aripiprazole.

- **Serious adverse events and deaths**

One death was reported in study 31-03-241 in an adolescent with schizophrenia. The event was an accidental electrocution (PT electrocution, SOC Injury, Poisoning and Procedural Complications), which was not attributed to study drug by the investigator.

There were no SAEs reported in pharmacokinetic studies 31-03-238 and CN138014.

Study 31-03-239

The percentage of subjects who experienced SAEs was similar across the 3 treatment arms: 4/100 (4.0%) and 4/102 (3.9%) in the aripiprazole 10 mg and 30 mg arms, respectively, and 3/100 (3.0%) in the placebo arm.

The most commonly reported SAEs overall were psychotic disorder (3 subjects, 1 in each treatment arm) and schizophrenia (2 subjects, 1 in each aripiprazole treatment arm).

In the aripiprazole 10 mg arm, the following SAEs were reported by 1 subject each in the aripiprazole 10 mg arm: extrapyramidal disorder, possible neuroleptic malignant syndrome, aggression, psychotic disorder, schizophrenia, and thrombophlebitis.

In the aripiprazole 30 mg arm, the following SAEs were reported by 1 subject each: varicella, depression, psychotic disorder, schizophrenia, and suicidal ideation.

In the placebo arm, intentional overdose, overdose, psychotic disorder, and suicide attempt were reported by 1 subject each.

Study 31-03-24

A total of 14/239 (5.9%) subjects with schizophrenia experienced SAEs. The majority of these SAEs were severe in intensity.
The following SAEs were reported by 1 subject each: acute bronchitis, hepatitis A, electrocution, intentional overdose, acute psychosis, auditory hallucination, homicidal ideation, impulsive behavior, intentional self-injury, and suicidal ideation.

Overall, 5 subjects with schizophrenia reported SAEs resulting in premature discontinuation of study medication: psychotic disorder (n=2), electrocution (n=1), acute psychosis (n=1), and auditory hallucination (n=1).

Study 31-05-243

Overall, 5 (5.9%) subjects experienced SAEs during the study. Suicide attempt was reported by 2 subjects, considered unrelated or not likely to be related to study medication.

One subject experienced severe psychomotor hyperactivity and aggression that were both classified as serious. The remaining SAEs reported by one subject each were ligament injury and worsening of schizophrenia.

- **Discontinuation due to adverse events**

Study CN138014

No subjects prematurely discontinued due to AEs.

Study 31-03-238

One subject, an 11-year-old black male with a psychiatric history of schizophrenia in the aripiprazole 25 mg cohort withdrew from the study because of an AE of moderate dystonia that was considered by the investigator to be definitely related to the study medication.

Study 31-03-239

A total of 13/302 (4.3%) subjects discontinued study medication due to TEAEs. The percentage of subjects who discontinued study medication due to TEAEs was greater in the aripiprazole 10 mg arm (7/100, 7.0%) than in the aripiprazole 30 mg arm (4/102; 3.9%) or the placebo arm (2/100, 2.0%).

The most commonly reported TEAEs resulting in discontinuation of study medication (reported by more than 1 subject overall) were psychotic disorder (1 subject in each treatment arm) and schizophrenia (2 subjects in the aripiprazole 10 mg arm and 1 subject in the aripiprazole 30 mg arm).

Study 31-03-241

A total of 6/239 (2.5%) subjects with schizophrenia discontinued study medication due to AEs. The majority of these AEs were moderate to severe in intensity. The reasons for discontinuation were leukopenia, electrocution, acute psychosis and auditory hallucination in one subject each (0.4%), as well as psychotic disorder in 2 subjects (0.8%).

Study 31-05-243

Four subjects (4.7%) discontinued study medication due to SAEs: suicide attempt (2 subjects), aggression (1 subject), and schizophrenia (1 subject).

- **Discussion on clinical safety**

The safety profile from the five clinical studies conducted in children and adolescent populations appeared to be similar to the one observed in the adult population.

In the short-term placebo-controlled clinical trial involving 302 adolescents (13-17 years) with schizophrenia, the frequency and nature of undesirable effects were similar to those in adults except for the following events that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo): somnolence/sedation and extrapyramidal disorders were reported very commonly, and dry mouth, increased appetite, and orthostatic hypotension were reported commonly.

The CHMP considered that the lack of long term data do not allow to make any conclusions, particularly for the high rate of EPS symptoms and of weight gain and the effects on sexual maturation, growth, metabolism and suicidality, that have been identified as concerns for other antipsychotics.

The MAH argued that on the basis of available paediatric data (studies 31-03-239 and 31-03-241) for aripiprazole, there is no increased reporting of EPS in comparison to other atypical antipsychotics nor a high rate of weight gain associated with aripiprazole. Furthermore, the MAH considered that there were no signals observed in clinical trials indicating an increased risk for suicidality with aripiprazole treatment.

The long-term open-label study 31-05-243 is ongoing. An interim analysis with a clinical data cut-off date of 1 June 2008 has been conducted to provide data on growth and sexual maturation. On the basis of this analysis and data from study 31-03-239, the MAH concluded that there is no signal of a negative influence of aripiprazole on growth or sexual maturation in adolescent patients.

However, the CHMP was of the opinion that further proactive data should be collected for the following safety concerns: EPS symptoms, weight gain, suicidality, growth and sexual maturation.

At the SAG CNS meeting held on 5 February 2009, the experts were also requested to discuss the main safety concerns identified with antipsychotics intended to be used in the treatment of schizophrenia in the adolescent population in the context of long term safety and concluded the following:

- Considering long term safety, 2 to 5-year observational studies are viewed as clinically meaningful to allow adequate collection of clinical data in adolescents on cognition (developmental aspects), social adjustment, suicidality, sexual maturation, weight gain and metabolic adverse effects, as well as on EPS/akathisia.

At the follow up SAG held on 11 May 2009, the experts considered that:

- Pre-authorisation long-term safety studies should address at least the most important (suicidality) or most common (EPS, weight gain, amenorrhea) or most specific (impact on cognition, memory, executive functions) safety risks. These will not exclude a comprehensive appraisal of rare situations *via* post-marketing studies in the frame of the Risk Management Plan.

- Reasonable study duration is estimated 2-year. For the assessment of adverse effects for which signals have been caught (see above) it is critical that specific studies are implemented. It was mentioned that collected data could be also analysed versus healthy controls cohorts.
To assess suicidality, a well identified and meaningful risk in the adolescent age group, the Columbia University scale and questionnaire can be used but other validated tools may be considered.
Finally, for cognitive impact, if on one hand the current knowledge does not allow to ask for predefined improvements in cognitive domains, on the other hand the Experts agreed that possible deterioration should also be investigated. If a specific cognitive improvement is expected this should adequately investigated.

Taking into consideration the SAG conclusions, the CHMP recommended that the prospective safety data should cover a minimum period of 2 years. The CHMP also recognised that there are risks that although important are extremely difficult to be evaluated in practice like the impact in cognition for example.

Following the CHMP's view, the MAH agreed to conduct a number of pooled analysis from paediatric placebo-controlled completed studies and from ongoing studies (as post authorisation commitments) to further investigate these concerns, as follows:

- a pooled analysis on prolactin levels, height, weight, lipid parameters, glucose, insulin and ECGs of the following studies performed in adolescent schizophrenia patients (13-17 years) for up to two years: 31-03-239, 31-03-241 and 31-05-243;
- a pooled analysis on prolactin levels, height, weight, lipid parameters, glucose, insulin and ECGs of the studies performed in children and adolescents (10-17 years) with bipolar I disorder for up to 32 weeks: 31-03-240 and 31-03-241;
- data analysis on prolactin levels, height, weight, lipid parameters, glucose, insulin, ECGs and Tanner staging for study CN138-180 conducted in children and adolescents (6-17 years) with autistic disorder for up to 1 year.

In accordance with the updated RMP, prospective safety data will be collected over 2-years exposure in adolescent schizophrenia patients (13-17 years).

Furthermore, the MAH also agreed to conduct an epidemiologic cohort study to assess suicide in adolescent patients using aripiprazole as post-authorisation commitment.

Having considered the above, the CHMP considered that the proposed follow up measures were adequate to ensure a safe use of the product in the proposed new indication.

4. Pharmacovigilance

The MAH submitted a revised RMP (version 4.2).

The submitted RMP is summarised in Table 4.

Table 4. Safety concerns, proposed Pharmacovigilance (PV) actions, and Proposed Risk Minimisation Activities

Safety Concern	Proposed PV Activities	Proposed Risk Minimization Activities (Routine and Additional)
Important Identified Risks:		
EPS, including tardive dyskinesia	Routine PV as listed in the current RMP Proposed PV Activities: 1. To conduct meta-analyses of all existing pediatric data to evaluate safety concerns among aripiprazole treated pediatric patients with schizophrenia (patients aged 13 to 17 years), with bipolar disorder (patients aged 10 to 17 years) and with autistic disorder (patients aged 6 to 17 years). 2. To conduct a prospective study to collect data in adolescent patients receiving aripiprazole for up to 2 years' duration.	Warnings & Precautions, section 4.4 of SPC: Tardive dyskinesia: in clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or can even arise after discontinuation of treatment. Undesirable effects, section 4.8 of SPC: incidence rates listed for aripiprazole versus active comparators or placebo for bipolar mania program: "Nervous system disorders - Common: extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache.
NMS	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SPC: Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may

		include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including ABILIFY, must be discontinued."
Important Potential Risks:		
Seizures	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SPC: Seizure: in clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures."
Hyperglycemia/ diabetes	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SPC: Hyperglycaemia and diabetes mellitus: hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotic agents, including ABILIFY. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control.
Suicide	Routine PV as listed in the current RMP plus epidemiological claims database study of the association of use	Warnings & Precautions, section 4.4 of SPC: The occurrence of suicidal behaviour

	of atypical antipsychotics and the incidence of suicide events (CN138458) , the original epidemiology suicidality study in adult patients, and CN138537, the extension study). Plan to conduct an epidemiological cohort study to assess suicide in adolescent patients using aripiprazole (Appendix 4)	is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study found that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with bipolar disorder." Undesirable effects, section 4.8 of SPC: Psychiatric disorders: agitation, nervousness; suicide attempt, suicidal ideation, and completed suicide (see section 4.4)."
Orthostatic Hypotension	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SPC for ABILIFY solution for injection: Patients receiving aripiprazole solution for injection should be observed for orthostatic hypotension. Blood pressure, pulse, respiratory rate and level of consciousness should be monitored regularly."
Dyslipidemia	Routine PV as listed in the current RMP and Proposed clinical data analysis	None
Important Missing Information		
Pregnancy and Lactation	Routine PV as listed in the current RMP	Pregnancy and lactation, section 4.6 of SPC: There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus. Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breastfeed if they are taking aripiprazole."

Pediatrics	Routine PV as listed in the current RMP Proposed PV Activities: 1. To conduct meta-analyses of all existing pediatric data to evaluate safety concerns among aripiprazole treated pediatric patients with schizophrenia (patients aged 13 to 17 years), with bipolar disorder (patients aged 10 to 17 years) and with autistic disorder (patients aged 6 to 17 years). 2. To conduct a prospective study to collect data in adolescent patients receiving aripiprazole for up to 2 years' duration	Therapeutic indications for paediatric patients in section 4.1 of the SPC: ABILIFY is indicated for the treatment of schizophrenia in adolescents (15 - 17 years)." Posology and method of administration, section 4.2 of the SPC: ABILIFY is not recommended for use in patients below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1)."
Other Potential Concerns		
Cardiovascular-related disorders (primarily applies to elderly patients with dementia-related psychosis)	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SPC: Cardiovascular disorders: Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant.
Conduction abnormalities (incidence of QT prolongation comparable to placebo)	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SPC: Conduction abnormalities: In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.
Weight gain (no statistically significant differences in weight gain/loss in bipolar mania)	Routine PV as listed in the current RMP Proposed PV Activities: 1. To conduct meta-analyses of all existing pediatric data to evaluate safety concerns among aripiprazole treated pediatric patients with schizophrenia (patients aged 13 to 17 years), with bipolar disorder (patients aged 10 to 17 years) and with autistic disorder (patients aged 6 to 17 years). 2. To conduct a prospective study to collect data in adolescent patients receiving aripiprazole for up to 2 years' duration	Warnings & Precautions, section 4.4 of SPC: Weight gain: weight gain is commonly seen in schizophrenic and bipolar mania patients due to co-morbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed ABILIFY. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain (see section 5.1)."

Growth	Proposed PV Activities: 1. To conduct meta-analyses of all existing pediatric data to evaluate safety concerns among aripiprazole treated pediatric patients with schizophrenia (patients aged 13 to 17 years), with bipolar disorder (patients aged 10 to 17 years) and with autistic disorder (patients aged 6 to 17 years). 2. To conduct a prospective study to collect data in adolescent patients receiving aripiprazole for up to 2 years' duration	None
Dysphagia (primarily applies to schizophrenia population)	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SPC: Dysphagia: oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including ABILIFY. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia."
Lactose (not new risk for bipolar mania)	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SPC: Lactose: ABILIFY tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product."
Drug interactions (not new risk for bipolar mania)	Routine PV as listed in the current RMP	Drug interaction information in section 4.5 of the SPC: 1.CYP2D6, 3A4 2.Antihypertensives 3.Alcohol or other CNS medications 4. Drugs prolonging QT or causing electrolyte imbalance 5. H2 antagonist
Increased mortality and CVA in elderly patients with dementia	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SPC: Elderly patients with dementia-related psychosis: Increased mortality: in three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56 99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in aripiprazole-treated patients was 3.5% compared to 1.7% in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature. Cerebrovascular adverse reactions: in the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients

		(mean age: 84 years; range: 78 88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6% of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole. ABILIFY is not indicated for the treatment of dementia-related psychosis.".
Serious Injection Site Reactions (with Solution for Injection only)	Continue monitoring post-marketing Adverse Events reports	None
Serious Hypersensitivity Reactions to Excipients (with Solution for Injection only)	Continue monitoring post-marketing Adverse Events reports	None

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

5. User Consultation

The MAH referred to the Readability Testing of the aripiprazole tablets Package Leaflet (PL) conducted during the assessment of the initial marketing authorisation application.

The MAH considered that the key safety information differences concerns adverse drug reactions already listed in the PL and that the layout is not significantly changed. This justification was considered acceptable by the CHMP.

6. Overall conclusions and benefit-risk assessment

Results from study 31-03-239, a large randomised controlled trial conducted in adolescents, with a mean age around 15, showed that aripiprazole was effective in the treatment of schizophrenia in this target population at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared with placebo in the primary efficacy endpoint, PANSS Total Score at Week 6 (LOCF).

Aripiprazole 10 mg and 30 mg were effective at Week 6 in the treatment of schizophrenia in adolescents based on statistically significant improvements compared with placebo in secondary efficacy endpoints (LOCF) that included change from baseline in PANSS Positive Subscale Score, CGAS Score, and CGI-Severity Score, and mean CGI-Improvement Score.

With respect to the long-term data, only open label studies were performed. The lack of active comparator and the open label design make the results of the submitted extension studies difficult to interpret.

Having requested several experts' views on these concerns, the CHMP considered that extrapolation from the adult to the adolescent population was still questionable, although it was expectable that the older adolescent group might be closer to the adult population.

At the oral explanation held on 20 July 2009, the MAH presented adolescent data (15-17 years) indicating similar acute and long-term efficacy results compared to adults. In addition, to address the validity of the extrapolation of long-term efficacy from adult data, the MAH provided comparative analysis between a subgroup of adult patients, with early episode of schizophrenia (characterised by: age < 40 years and shorter duration of disease i.e. ≤ 5 years since first episode) showing similar baseline PANSS score of 95.0 and 93.4 for adults and adolescents, respectively and the percentage of patients with treatment response was comparable in these populations.

On the other hand, the safety profile from the five clinical studies conducted in children and adolescent populations appeared to be similar to the one observed in the adult population. However, the CHMP considered that the lack of long term data do not allow to make any conclusions, particularly for the high rate of EPS symptoms and of weight gain and the effects on sexual maturation, growth, metabolism and suicidality, that have been identified as concerns for other antipsychotics.

Having requested several experts' views on these concerns, the CHMP considered that further proactive data should be collected in terms of safety concerns (e.g EPS symptoms, weight gain, suicidality, growth and sexual maturation) and recommended that the prospective safety data should cover a minimum period of 2 years.

Following the CHMP's view, the MAH agreed to conduct a number of pooled analysis from paediatric placebo-controlled completed studies and from ongoing studies (as post authorisation commitments) to further investigate these concerns. In addition, in accordance with the updated RMP, prospective safety data will be collected over 2-years exposure in adolescent schizophrenia patients (13-17 years). To specifically address the concern over suicidality, the MAH agreed to conduct an epidemiologic cohort study to assess suicide in adolescent patients using aripiprazole as post-authorisation commitment.

Having considered the above, the CHMP considered the proposed indication approvable provided that:

- The paediatric population is restricted to adolescents older than 15 year-old;
- Long-term efficacy and safety studies to further support the maintenance of the effect and to better characterise the safety profile in the adolescent population are performed by the MAH, as part of post-authorisation commitments.

Therefore, the CHMP concluded that the benefit risk assessment of Abilify in the proposed indication (new text= underlined), *"ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older."* is positive and recommended by majority, the variation to the Marketing Authorisation, subject to post-authorisation commitments related to long term efficacy and safety.