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EMA/62007/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Abilify

International non-proprietary name: aripiprazole

Procedure No. EMEA/H/C/000471/II/0082

Note

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

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1. Scientific discussion

1.1. Introduction

Bipolar disorders are severe and most often chronic mental illnesses. They are associated with considerable morbidity and mortality, and for many patients an initial episode of mania or depression evolves into a life long illness (*Bauer and Pfennig 2005*). Of those who recover, up to 80% will experience one or more syndromal recurrences over a period of 2 to 5 years (*Birmaher et al. 2009, Geller et al. 2008*). Factors associated with worse longitudinal outcome include early age at illness onset, long illness duration, mixed episodes, rapid cycling, psychosis, subsyndromal symptoms, comorbid disorders, low socioeconomic status, exposure to negative life events, lack of psychotherapy treatment, poor adherence to pharmacological treatment, and family psychopathology (*Birmaher et al. 2009*).

Although there has been substantial research on the epidemiology of bipolar disorders in children and adolescents, there is still a striking lack of information on estimates of the prevalence and distribution of mental disorders generally in children. However, the lifetime prevalence rates for bipolar disorder estimated in a number of cross-sectional surveys have ranged from 0.4 to 1.9% for mania (*Merikangas et al. 2009*).

The clinical differentiation of bipolar I disorder and in particular early-onset mania from other severe psychiatric conditions below age 10, such as Attention Deficit Hyperactivity Disorder (ADHD), Conduct Disorder (CD), and Oppositional Defiant Disorder (ODD), can be complicated and unreliable. In children and adolescents, bipolar disorder is characterized by elevated mood and other mood disturbances, aggression, irritability, and hyperactivity. Additional symptoms can include extreme emotional outbursts, depression, social withdrawal, and sleep disturbances. Bipolar disorder in both children and adolescents is cyclical with high rates of rapid cycling and patients most often present with mixed episodes (primarily irritability and explosiveness). Children with bipolar disorders can often have a protracted, chronic course of illness that is difficult to treat. The degree of impairment and dysfunction often results in the loss of social and educational opportunities and thus has a lifelong impact for the patients (*AACAP 2007*).

Current guidelines for the treatment of children and adolescents with bipolar disorder recommend first-line treatment with atypical antipsychotics or mood stabilizers (*AACAP 2007*). By 2007, the recommendation was based on data available for those agents for bipolar disorder in adults, as evidence for the efficacy for these agents in children and adolescents was sparse. Despite the significant rise in the recognition of paediatric bipolar disorder and the use of antipsychotic agents, there remained a lack of data from randomized, placebo-controlled trials to guide treatment decisions. The clinical development program undertaken by the applicant was intended to address this lack of sounding evidence by investigating the efficacy and safety of aripiprazole in this patient population.

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

"ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder in adults **and in children and adolescents aged 10 years and older.**"

During the evaluation, the MAH proposed to restrict the proposed indication to Bipolar I Disorder in children and adolescents aged 13 years and older.

1.2. Non clinical aspects

No new non clinical data were submitted. An updated environmental risk assessment was submitted and results are summarised in Table 1.

Ecotoxicity / environmental risk assessment

Table 1 Summary of main study results

Substance (INN / Invented Name): Aripiprazole			
CAS-number (if available): 129722-12-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	FDA Guideline 3.02 (shaker-flask method)	pH 5 – 2.70 pH 7 – 2.95 pH 9 – 2.89	Potential PBT - No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	pH 5 – 2.70 pH 7 – 2.95 pH 9 – 2.89	not B
Persistence	DT50 or ready biodegradability	Not readily biodegradable	P
Toxicity	NOEC	*Daphnia* $NOEC_{reproduction}$ = 2.61 µg/L	T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{sw} , default	0.15	µg/L	> 0.01 threshold - Yes
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	FDA Guideline 3.08 Screening Test	K_{oc} =10270 (purified water) K_{oc} =2850 (0.01 M $CaCl_2$)	
Adsorption-Desorption	OECD 106	K_{Foc} =10900 (activated sludge) K_{Foc} =21700-10600 (4 soils)	High affinity for activated sludge and the test soils (incubation in 0.01 M $CaCl_2$)
Ready Biodegradability Test	FDA Guideline 3.11 (similar to 301B)	Negligible mineralization to CO_2 (0.034% over 42 days). ~10% primary degradation by day 38.	Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ =0.43 and 6.47 days $DT_{50, sediment}$ =Not obtained due to poorly defined declines in this compartment $DT_{50, whole\ system}$ =30.9 and 177 days	Data are from 2 different aquatic sediment systems. As aripiprazole was present in the sediment at greater than 10% by day 14, a chironomid study was

		% shifting to sediment =maximum of 89 and 96.6% (total radioactivity after 100 days)			conducted.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	140	µg/L	*Pseudokirchneriella subcapita;* NOEC based on growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	2.61	µg/L	NOEC is based on reproduction
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC-Survival	5.8	µg/L	Fathead minnow
		NOEC – Growth	13.6		
		NOEC – Hatching Success	213		
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50}	>1000	mg/L	
Phase IIb Studies					
Bioaccumulation	Not Required based on log K_{ow} value				
Aerobic and anaerobic transformation in soil	OECD 307	DT50	210	days	
		$\%CO_2$	2.3%	%	
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	0% inhibition at 2000	mg/kg	No inhibition at 2000 mg/kg
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	100	mg/kg	6 species; seedling emergence
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	1000	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC – mortality	0.150	mg/kg	
		NOEC - reproduction	>0.50		
Sediment dwelling organism	OECD 218	NOEC	100	mg/kg	Chironomids (*Chironomus riparius);* NOEC is for emergence and reproduction

Kow: n-octanol/water partition coefficient, PBT: Persistent, Bioaccumulative and Toxic, vPvB: very persistent and very bioaccumulative, PEC: Predicted Environmental Concentration, Koc, Kfoc: adsorption coefficients, DT50: Half-life of active, NOEC: No Observed Effect Concentration, EC50 : concentration of tested substance which inhibits the oxygen uptake by 50%, sw: surfacewater.

Discussion on non clinical aspects

No new non clinical data were submitted and this was considered acceptable by the CHMP as relevant information related to juvenile animal studies had already been submitted in the context of the approved variation extending the indication to the treatment of schizophrenia in adolescents 15 years and older (EMA/H/C/471/II/48) and reflected in the latest approved SmPC for Abilify.

Regarding the ERA, the CHMP agreed that no screening for persistence, bioaccumulation and toxicity is required since the Log K_{OW} is <4.5. In addition based on the lower Kow value (<1000) a bioconcentration study in fish is not considered necessary.

The data submitted regarding the water sediment study (OECD 308) suggested significant shifting of the drug substance to the sediment (from day 14 on more than 10% of aripiprazole was present in sediment extracts), and because aripiprazole does not seems to be ready biodegradable (OECD 308 and FDA 3.11 studies), the study of the effects on sediment organisms, namely Chironomids, was conducted in tier B analysis. This study (OECD 308) also suggested that aripiprazole does not have adverse effects on microbial activity, but a dose response relationship cannot be established.

From the data submitted regarding screening sorption/desorption studies on aripiprazole partition to sludge, the CHMP agreed that the data indicates significant sorption to organic carbon in sludge with a Koc>10 000 L/kg which implies that an environment assessment of the drug substance in terrestrial compartment should be conduct unless readily biodegradable, which does not seems to be the case. A tier B terrestrial analysis was conducted. By comparing the PECsoil (0.000974 mg/kg) with the Predicted No Effect Concentrations in soil (PNECsoil) obtained with the lowest NOEC (Collembolan reproduction) from the full battery of terrestrial studies the applicant concluded that the soil (terrestrial) is not impacted by aripiprazole entering the environment.

In addition the aquatic and sediment compartments did not show any impact from patient use of aripiprazole considering the following indications: schizophrenia (authorised in the EU), bipolar disorder including paediatric population (only authorised in adults in the EU), and Major Depressive Disorders (not authorised in the EU) as the corresponding PEC/PNEC ratios are below the threshold value. However the surface water compartment PEC/PNEC ratio below one was only achieved when further PECsw refinement was applied in tier B to account for sewage treatment plant removal using the adsorption data and the output from simple treat model, giving a PECsw.refined value of 5.524 x 10-8 mg/L instead of 2.668 x 10-4 mg/L.

It is worth noting that the revised PEC value of 0.2668 µg/L corresponds to 76% (because of the human metabolism) of the PEC value obtained using a refined Fpen value of 0.0234. This higher refined Fpen than the default one, was calculated using annual prevalence of bipolar disorders (1% includes the target pediatric population of this application), of schizophrenia (0.35%) and of MDD (1%)). In addition there is no requirement to refine the default Fpen, and there is no requirement to use a refined Fpen when it is above the default value, as in this case. If the PECsw value (0.15 µg/L) obtained with default Fpen (1%) value is used the PEC/PNECsw ratio obtained is below 1 (0.58). So it is likely that the margin between PEC and PNEC to be considerable higher as the PECsw was estimated very conservatively, using a Fpen higher than the default one and not accounting for depletion via sorption to sludge in a sewage treatment plant, it is therefore not expected that aripiprazole should pose a risk to the surface water compartment.

Finally, the precautionary and safety measures taken in order to reduce any risk to the environment by including the general statement on the SmPC and PL have been applied which is considered acceptable by the CHMP.

1.3. Clinical aspects

The development program completed to support the proposed extension of indication 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**);

- a phase III, multicenter, randomized, double-blind, placebo-controlled, 4 week study (**31-03-240**) of two fixed oral doses of aripiprazole 10 mg and 30 mg in the treatment of child and adolescent patients, aged 10-17 years, with bipolar I disorder, manic or mixed episode with or without psychotic features with a 6 month extension period;

- a phase III, multi-center, open-label (**study 31-03-241**) designed to provide additional long term safety data of aripiprazole in the paediatric population. Patients who had completed study 31-03-239 (adolescents with schizophrenia) or had withdrawn from the double blind study 31-03-240 were offered to continue in the open-label, flexible-dose study 31-03-241 for an additional 26 weeks.

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

All of the above studies were previously submitted to the CHMP. Studies 31-03-238, CN138014, 31-03-240 and 31-03-241 were submitted in the context of the approved variation extending the indication to the treatment of schizophrenia in adolescents 15 years and older (EMA/H/C/471/II/48) and study 31-03-240 was submitted in accordance with the article 46 of the Paediatric Regulation 1901/2006.

The applicant claimed that the above clinical development program has been designed in accordance with the “Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Bipolar Disorder”, (CPMP/EWP/567/98).

1.3.1. Pharmacokinetics

Based on studies 31-03-238 and CN138014, the linearity of the pharmacokinetic parameters of aripiprazole in children and adolescents was 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.

Given the similar pharmacokinetic profile, the main efficacy study 31-03-240 investigated the full range of available doses by testing the 10 mg and 30 mg doses (see further discussion on 2.3.2.4).

1.3.2. Clinical efficacy

1.3.2.1. Main efficacy study

Study 31-03-240 is the main efficacy study to support the indication applied for and was submitted in accordance with the article 46 of the Paediatric Regulation 1901/2006.

METHODS

Study design

This was a multicenter, randomized, 30 week double-blind, placebo-controlled Phase III clinical trial conducted in 59 centres in the United States (US).

Objective

The objective was to assess the efficacy and safety of two fixed doses of aripiprazole (10 mg and 30 mg) compared to placebo in children and adolescents, aged 10 to 17 years, with a Diagnostic and Statistical Manual IV (DSM-IV) diagnosis of bipolar I disorder, manic or mixed episode with or without psychotic features.

Main inclusion criteria

Male and female subjects, 10 to 17 years of age, with a manic or mixed episode associated with bipolar I disorder were eligible to participate in this study.

The main inclusion criterion was a DSM-IV diagnosis of bipolar I disorder, manic or mixed episode, with or without psychotic features (American Psychiatric Association, 1994). The DSM-IV diagnosis was also independently confirmed by a separate, trained clinician administering the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1996), which is a semi-structured interview of patients and parents/caregivers by an adequately trained clinician. Co-morbid diagnoses were permitted including Attention Deficit Hyperactivity Disorder (ADHD), Conduct Disorder (CD), Oppositional Defiant Disorder (ODD), and anxiety disorders (except Post Traumatic Stress Disorder [PTSD] and Obsessive Compulsive Disorder [OCD]).

The initial diagnosis was made by an adequately trained clinician (ie, board certified child and adolescent psychiatrist [CAP] or board eligible CAP), and then confirmed by an adequately trained utilizing the Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime Version (K-SADS-PL) at screening.

Treatment period

There were two phases in this study, a 4-week acute phase and a 26-week extension period. Each subject had the potential to participate in this study for a total of up to 30 weeks of double-blind treatment, including a 4-week acute phase with a 6-month extension period, preceded by a screening phase of up to 28 days.

Both phases of the study could be conducted either on an outpatient basis (with the option for inpatient hospitalization, if needed), or in a partial or full inpatient basis at any given time of the study.

On Day 1 of the acute Phase, subjects were randomized to either 10 mg or 30 mg of oral aripiprazole or placebo treatment. Subjects reached their target dose through a forced titration schedule of up to 13 days and proceeded with treatment at their target dose.

If the subject reached week 4 of the acute Phase, they continued into the extension phase, a 26-week double-blind treatment period, beginning at the same dose as taken at the end of the acute phase. The investigator had the option to down-titrate a subject's dose only one time during the extension phase to half the target dose for tolerability reasons. Following a dose reduction, investigators could also up-titrate one time as needed to enhance efficacy to 20 mg from 15 mg in the 30 mg arm, and to 10 mg from 5 mg in the 10 mg arm. Subjects who discontinued during the acute phase for lack of efficacy, or for any reason, were offered an alternative rescue medication for 4 to 8 weeks.

Subjects who received at least one dose of study medication in the extension Phase of the study were eligible to roll-over to an open-label study (Study No. 31-03-241) if they dropped out of this phase due to tolerability reasons.

Primary efficacy endpoint

The primary efficacy variable is the change from baseline to week 4 in the Young Mania Rating Scale (YMRS) Total Score. Subjects who completed the week 4 visit were defined as completers of the acute phase.

Secondary efficacy endpoints

Secondary efficacy variables included the change from baseline (evaluated at each visit up to 30 weeks) in the YMRS total score; the Children's Global Assessment Scale (CGAS) score, the clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity score; the Children's Depression Rating Scale-Revised (CDRS-R) score, the General Behavior Inventory Scale (GBI) score; the Attention Deficit Hyperactivity Disorders Rating Scale (ADHD-RS-IV) score and Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-Q-LES-Q translated into different languages when applicable).

In addition, subject response to treatment (defined as a 50% or higher reduction from baseline in Y-MRS total score); change from preceding phase score on the CGI-BP and P-Q-LES-Q; time to discontinuation due to all reasons were also measured as secondary efficacy variables.

Subjects who completed the week 30 visit were defined as completers for the entire study.

Statistical method

The core data set for all efficacy analyses was the intent-to-treat (ITT) dataset, which contains data from all randomized subjects. In order to handle missing data and restrictions imposed by different types of analyses (e.g., change from baseline analysis), other data sets derived from the ITT data set were used for the efficacy analyses, such as the observed cases (OC) data set and the last observation carried forward (LOCF) datasets as described below.

For change from baseline analysis, only subjects who had both baseline and post-baseline values were included in the OC and LOCF data sets. LOCF data sets were the primary analysis data sets. The OC data set corresponding to a visit consists of data from all subjects who were evaluated at that visit on the efficacy variable under analysis, i.e., subjects with missing data due to dropout or other reasons were not included in the OC data set. In the LOCF data set, missing data at a post-baseline visit were imputed with the value obtained at the nearest preceding visit, except that baseline values were not carried forward to impute missing values at a post-baseline visit.

Nominal overall significance level of 0.05 (two-tailed) was used in testing the statistical significance of the comparisons between aripiprazole 10 mg target dose versus placebo and aripiprazole 30 mg target dose versus placebo. For the primary treatment comparisons of a dose group versus placebo, adjustment in testing due to multiple comparisons was handled by an overall F-test. Descriptive statistics for the YMRS Total Scores and change from baseline scores were presented by treatment group for week 1 through week 4 for both OC and LOCF datasets. The change scores were analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor, and baseline YMRS Total Score as a covariate. For comparing YMRS Total Scores between treatment groups at Baseline, only treatment was included in the analysis of variance (ANOVA) model with baseline value as the dependent variable. The least squares (LS) means obtained from a type III analysis using SAS were used for the treatment comparisons. Two-tailed student's t-tests were used to test differences between the LS means within the ANCOVA or ANOVA model.

The CGAS, CGI-BP severity, CDRS-R, GBI, ADHD-RS-IV, and P-QLES-Q Total Score were analyzed similarly to the YMRS. The proportion of subjects responding to treatment was analyzed using a chi-square test, with 95% confidence intervals for differences in response rates. Changes from the preceding phase score in the CGI-BP and P-QLES-Q overall score were analyzed using the Cochran-Mantel-Haenszel row mean score statistic by week. Time to discontinuation was analyzed by plotting the Kaplan-Meier curves and testing for significance of the differences in survival curves using the log-rank test for each active group versus the placebo group.

Sample size

The study is designed to have 85% power given a difference between aripiprazole and placebo of -5.1 for the change from baseline in Y-MRS total Score at week 4 (LOCF). The difference of -5.1 was estimated from two bipolar mania trials in adult populations. A pooled standard deviation of 11.1 was used in these computations. Based on these estimates and using a two-sided alpha of 0.025, 87 patients per treatment arm with a total 261 patients are required for 85% power. An evaluable patient is defined as one having a baseline and a post-baseline value of Y-MRS total assessment. Maximum 300 patients were to be enrolled for screening to maintain the power of the study.

RESULTS

Patient distribution

A total of 296 subjects were randomized: 98/296 (33.1%) in the aripiprazole 10 mg arm, 99/296 (33.4%) in the aripiprazole 30 mg arm, and 99/296 (33.4%) in the placebo arm.

Age distribution is presented in Table 2.

Table 2. Age distribution

Number of subjects				
Age	Aripiprazole 10 mg	Aripiprazole 30 mg	Placebo	Total
10	**10**	**16**	**12**	38
11	**8**	**9**	**9**	26
12	**14**	**13**	**18**	45
13	**12**	**14**	**17**	43
14	**13**	**11**	**14**	38
15	**19**	**7**	**9**	35
16	**10**	**16**	**12**	38
17	**12**	**9**	**8**	29

All randomized subjects were included in the efficacy analyses (randomized subjects evaluated for at least one primary or secondary efficacy parameter).

A high rate of retention (237/296 [80.1%] subjects overall) was observed for the acute phase of the study: 84/98 (85.7%) in the aripiprazole 10 mg arm, 77/99 (77.8%) in the aripiprazole 30 mg arm, and 76/99 (76.8%) in the placebo arm.

A total of 68/296 (23.0%) subjects completed the entire study: 34/98 (34.7%) in the aripiprazole 10 mg arm, 22/99 (22.2%) in the aripiprazole 30 mg arm, and 12/99 (12.1%) in the placebo arm.

Subject disposition is presented in Table 3.

Table 3 Subject disposition

	Acute Phase (4 weeks)			Acute and Maintenance Phase (4 weeks + 26 weeks)		
Subjects	Aripip 10 mg **(N = 98)**	Aripip 30 mg **(N = 99)**	Placebo **(N = 99)**	Aripip 10 mg **(N = 98)**	Aripip 30 mg **(N = 99)**	Placebo **(N = 99)**
Randomized	**98 (100.0)**	**99 (100.0)**	**99 (100.0)**	**98 (100.0)**	**99 (100.0)**	**99 (100.0)**
Completed[a]	**84 (85.7)**	**77 (77.9)**	**76 (76.8)**	**34 (34.7)**	**22 (22.2)**	**12 (12.1)**
Discontinued	**14 (14.3)**	**22 (22.2)**	**23 (23.2)**	**64 (65.3)**	**77 (77.8)**	**87 (87.9)**
Lost to follow-up	**3 (3.1)**	**3 (3.0)**	**5 (5.1)**	**5 (5.1)**	**5 (5.1)**	**11 (11.1)**
Adverse events	**4 (4.1)**	**7 (7.1)**	**1 (1.0)**	**9 (9.2)**	**19 (19.2)**	**2 (2.0)**
Investigator withdrew subject	**1 (1.0)**	**0**	**2 82.0)**	**8 (8.2)**	**9 (9.1)**	**9 (9.1)**
Subject withdrew consent	**4 (4.1)**	**9 (9.1)**	**6 (6.1)**	**20 (20.4)**	**28 (28.3)**	**21 (21.2)**
Protocol deviation	**0**	**1 (1.0)**	**1 (1.0)**	**3 (3.1)**	**3 83.0)**	**1 (1.0)**
Lack of efficacy[b]	**2 (2.0)**	**2 (2.0)**	**8 (8.1)**	**19 (19.4)**	**13 (13.1)**	**43 (43.4)**
Efficacy ITT[c]	**98 (100.0)**	**99 (100.0)**	**99 (100.0)**	**98 (100.0)**	**99 (100.0)**	**99 (100.0)**
Safety ITT[d]	**98 (100.0)**	**99 (100.0)**	**97 (98.0)**	**98 (100.0)**	**99 (100.0)**	**97 (98.0)**

Source: CT-1.1, CT-2.1 and CT-2.2 of Clinical Study Report 31-03-240
[a] Completers: Subjects who completed the Week 4 visit are defined as completers for the Acute Phase; subjects who completed the Week 30 visit are defined as completers for the Maintenance Phase
[b] as determined by the investigator
[c] Efficacy ITT: Randomized subjects evaluated for at least one primary or secondary efficacy parameter
[d] Safety ITT: Subjects receiving at least one dose of study drug
Aripi: aripiprazole

Baseline Characteristics

Overall baseline disease severity, as measured by YMRS Total Score, CDRS-R Suicidal Ideations Score, and treatment status for previous episodes, was comparable across all treatment arms. Table 4 summarised these results.

Table 4 Baseline disease severity

Baseline Characteristic	Statistic	Aripiprazole 10 mg (N = 98)	Aripiprazole 30 mg (N = 99)	Placebo (N = 99)	Total (N = 296)
YMRS Total Score	N Mean (SD)	98 29.8 (6.5)	99 29.5 (6.3)	99 30.7 (6.8)	296 30.0 (6.5)
CDRS-R Suicidal Ideation Score	N Mean (SD)	98 1.1 (0.4)	99 1.1 (0.5)	98 1.2 (0.5)	295 1.2 (0.5)
Treatment given for previous episodes	Yes, n (%) No, n (%))	57 (58.20) 41 (41.80)	50 (50.50) 49 (49.50)	63 (63.60) 36 (36.40)	170 (57.40) 126 (42.60)

Source: CT-3.2 of Clinical Study Report 31-03-240

A total of 53.4% of all patients included in this study used baseline medications prior to the start of the study. The most commonly used baseline medications (by ≥ 3% incidence overall) include ibuprofen, paracetamol, oxcarbazepine, valproate semisodium, salbutamol, methylphenidate, hydrochloride obetrol, lorazepam, Quetiapine and risperidone.

Efficacy Results

Results from efficacy endpoints are presented in Tables and Figures presented below.

Table 5 Short term efficacy results at week 4

Efficacy Endpoint	Treatment Group	Difference in Mean Change versus Placebo[a]	95% Confidence Interval	P-Value[b]
Primary Efficacy Endpoint				
YMRS Total[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-5.99 -8.26	-8.49; -3.50 -10.7; -5.77	< 0.0001 < 0.0001
Secondary Efficacy Endpoints				
CGAS[d]	Aripiprazole 10 mg Aripiprazole 30 mg	9.30 11.51	5.77; 12.84 7.99; 15.03	< 0.0001 < 0.0001
CGI-BP Severity - Mania[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-0.81 -1.26	-1.15; -0.48 -1.59; -0.93	< 0.0001 < 0.0001
CGI Severity - Depression[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-0.25 -0.26	-0.54; -0.04 -0.55; -0.03	0.0878 0.0752
CGI Severity – Overall Bipolar Illness[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-0.83 -1.18	-1.16; -0.51 -1.51; -0.86	< 0.0001 < 0.0001

Efficacy Endpoint	Treatment Group	Difference in Mean Change versus Placebo[a]	95% Confidence Interval	P-Value[b]
CDRS-Total[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-2.28 -1.19	-4.81; 0.25 -3.69; 1.32	0.0767 0.3515
GBI Total Parent/Guardian Version - Mania[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-5.88 -5.46	-8.02; -3.73 -7.60; -3.32	< 0.0001 < 0.0001
GBI Total Subject Version - Mania[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-1.85 -2.03	-3.67; -0.03 -3.85; -0.20	0.0468 0.0296
GBI Total Parent/Guardian Version - Depression[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-2.13 -0.31	-4.20; -0.07 -2.37: -1.76	0.0430 0.7696
GBI Total Subject Version - Depression[c]	Aripiprazole 10 mg Aripiprazole 30 mg	0.07 0.19	-1.73; -1.86 -1.61; -1.98	0.9418 0.8377
ADHD-RS-IV Total[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-8.86 -8.23	-12.3; -5.43 -11.6; -4.83	< 0.0001 < 0.0001
P-QLES-Q Total[d]	Aripiprazole 10 mg Aripiprazole 30 mg	1.16 2.45	-1.60; 3.93 -0.35; 5.24	0.4080 0.0858

[a] Least squares mean differences are derived from analysis of covariance model of change from baseline with baseline as covariate and terms for treatment
[b] The p-values were derived from Student's t-Tests on estimates of treatment comparison which were based on least square means
[c] A negative least square mean difference indicates improvement
[d] A positive least square mean difference indicates improvement
Source: CT-5.10.1.1 of Clinical Study Report 31-03-240

Table 6 Long term efficacy results at week 30

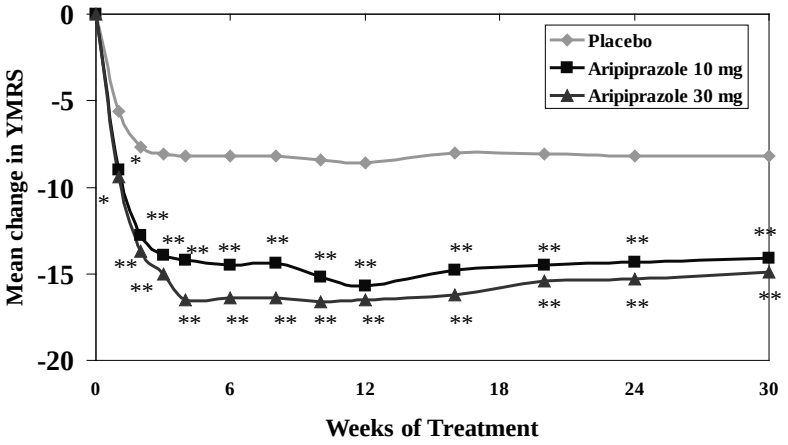
Efficacy Endpoint	Treatment Group	Difference in Mean Change versus Placebo[a]	95% Confidence Interval	P-Value[b]
Efficacy Endpoints				
YMRS Total[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-5.89 -6.73	-8.70; -3.08 -9.53; -3.94	< 0.0001 < 0.0001
CGAS[d]	Aripiprazole 10 mg Aripiprazole 30 mg	9.23 10.00	5.07; 13.39 5.87; 14.14	< 0.0001 < 0.0001

Efficacy Endpoint	Treatment Group	Difference in Mean Change versus Placebo[a]	95% Confidence Interval	P-Value[b]
CGI-BP Severity - Mania[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-0.70 -1.04	-1.08; -0.33 -1.41; -0.66	0.0003 < 0.0001
CGI Severity - Depression[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-0.19 -0.39	-0.51; -0.13 -0.71; -0.07	0.2552 0.0166
CGI Severity – Overall Bipolar Illness[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-0.76 -0.97	-1.13; -0.40 -1.33; -0.60	< 0.0001 < 0.0001
CDRS-Total[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-1.92 -0.43	-4.69; 0.85 -3.17; 2.31	0.1729 0.7586
GBI Total Parent/Guardian Version - Mania[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-4.76 -4.64	-6.90; -2.61 -6.78; -2.50	< 0.0001 < 0.0001
GBI Total Subject Version - Mania[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-1.44 -2.64	-3.31; -0.43 -4.51; -0.77	0.1309 0.0058
GBI Total Parent/Guardian Version - Depression[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-2.13 -1.27	-4.31; 0.04 -3.44; 0.91	0.0545 0.2524
GBI Total Subject Version - Depression[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-0.82 -1.21	-2.71; 1.08 -3.09; 0.68	0.3969 0.2101
ADHD-RS-IV Total[c]	Aripiprazole 10 mg Aripiprazole 30 mg	-7.05 -5.55	-10.5; -3.64 -8.94; -2.16	< 0.0001 0.0014
P-QLES-Q Total[d]	Aripiprazole 10 mg Aripiprazole 30 mg	1.20 2.17	-1.40; 3.79 -0.49; 4.82	0.3642 0.0014

[a] Least squares mean differences are derived from analysis of covariance model of change from baseline with baseline as covariate and terms for treatment
[b] The p-values were derived from Student's t-Tests on estimates of treatment comparison which were based on least square means
[c] A negative least square mean difference indicates improvement
[d] A positive least square mean difference indicates improvement
Source: CT-5.10.1.1 of Clinical Study Report 31-03-240

The mean change in YMRS Total Score from baseline for all visits is shown in figure 1.

Figure 1 mean change in YMRS Total Score from baseline for all visits



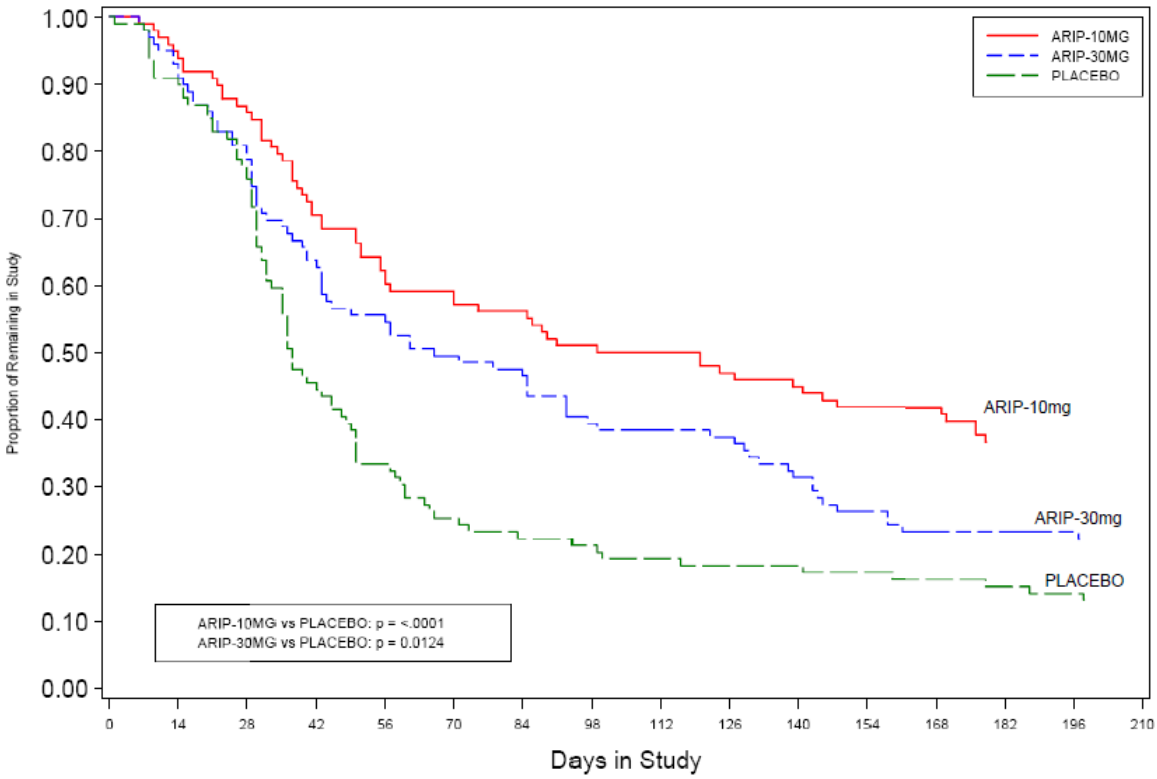
Baseline YMRS score = 30.1
LOCF analysis; *p < 0.05, **p < 0.0001

Table 7 Responder analyses at week 4 and 30

	N[a]	n[b]	%	P-Values[c]
Week 4				
Placebo	92	24	26.09	
Aripiprazole 10 mg	96	43	44.79	0.0074
Aripiprazole 30 mg	99	63	63.64	< 0.0001
Week 30				
Placebo	94	25	26.60	
Aripiprazole 10 mg	96	48	50.00	0.0009
Aripiprazole 30 mg	99	55	55.56	< 0.0001

[a] N = Number of randomized patients with both baseline and at least one post-baseline value
[b] n = number of responders
[c] P values are derived from Chi-square tests
Source: CT-5.9.1 of Clinical Study Report 31-03-240

Figure 2 – Kaplan-Meier Plot for Time to discontinuation due to all reasons up to 30 weeks



1.3.2.2. Supportive study

Study 31-03-241 was submitted in the context of the approved variation extending the indication to the treatment of schizophrenia in adolescents 15 years and older (EMA/H/C/471/II/48). It was designed to provide additional long term safety data of aripiprazole in the paediatric population. Patients who had completed study 31-03-239 (adolescents with schizophrenia) or had withdrawn from the double blind study 31-03-240 were offered to continue in the open-label, flexible-dose study 31-03-241 for an additional 26 weeks.

The results obtained in these two different patient populations were evaluated separately. For the purpose of the present application, only relevant methodological aspects and efficacy results obtained in the population of adolescents and children with bipolar I disorder who had withdrawn from study 31-03-240 are presented.

METHODS

Treatment period

Subjects enrolled in the study were eligible to receive up to a total of 6 months (cumulative with exposure in the parent study) of open-label aripiprazole treatment at daily doses of 2 mg to 30 mg. The open-label trial overlapped with the parent study 31-03-240 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.

On Day 0 of open-label treatment in Study 31-03-241, patients from all treatment groups of the parent study 31-03-240 received an up-titration blister card for treatment Days 1 through 6. Up-titration to the target dose of 10 mg was done in the following manner for all patients: Days 1 and 2: 2 mg/day; Days 3 and 4: 5 mg/day; Days 5 and 6: 10 mg/day. If the subject was unable to tolerate the titration during this fixed up-titration phase, the subject was withdrawn from the study. On Day 7, the investigator had the option to continue the dose escalation up to a maximum of 30 mg/day, or, for tolerability issues, to reduce the dose of aripiprazole to no less than 2 mg/day for subjects with bipolar I disorder. To escalate the dose, subjects received 15 mg for a minimum of 2 days, 20 mg for a minimum of 2 days, 25 mg for a minimum of 2 days, and then 30 mg for 2 days as the highest dose. Dose escalation could stop at any dose level that the investigator felt was tolerable for the subject. Dose reduction, if necessary based on clinical judgment in regard to tolerability, occurred at a rate that was considered by the investigator to be appropriate for the subject. Following the initial dose reduction, the investigator could escalate the subject's dose again based on clinical judgment at a rate that was considered by the investigator to be appropriate for the subject. Once a subject's dose had been escalated following the initial dose reduction, no further dose reductions were permitted. Failure to tolerate the medication after dose reduction to the minimal allowable dose level, or to the escalated dose level afterwards, resulted in removal of the subject from the study.

The open-label safety study was conducted on an outpatient basis with clinic visits at weeks 1, 2, 3, 4, 8, 12, 18, and 26.

Efficacy endpoints

The efficacy variables for subjects with bipolar I disorder (manic or mixed episode with or without psychotic features) were: mean change from Baseline on the YMRS score; the CGI-BP severity score; the GBI score and the ADHD-RS-IV score.

Other outcome variable included the P-QLES-Q Total score (translated into different languages when applicable). PL-QLES-Q was completed by each subject at Baseline (Day 0) and End of Treatment/Early Termination (week 26).

RESULTS

A total of 86 child and adolescent subjects with bipolar I disorder from the parent study 31 03 240 were enrolled receiving an average daily dose of aripiprazole of 15.1 mg (range 4.9 – 17.7 mg).

All 86 patients were included in the efficacy analysis. A total of 57 patients completed the study (see Table 8).

Table 8 Subject disposition

Subjects	N = (%)
Enrolled	86 (100.0)
Completed	57 (66.3)
Discontinued	29 (33.7)
Lost to follow-up	8 (9.3)
Adverse events	1 (1.2)
Subject met withdrawal criteria	1 (1.2)
Investigator withdrew subject	3 (3.5)
Subject withdrew consent	13 (15.1)
Protocol deviation	1 (1.2)
Lack of efficacy as determined by investigator	2 (2.3)
Efficacy ITT[a]	86 (100.0)
Safety ITT[b]	86 (100.0)

Source: CT-1.1 and CT-2 of Clinical Study Report 31-03-241
[a] Efficacy ITT: Enrolled subjects evaluated for at least one primary or secondary efficacy parameter
[b] Safety ITT: Subjects receiving at least one dose of study drug

The mean change from baseline in YMRS Total Score by week is presented in Table 9.

Table 9 Mean change from baseline in YMRS Total Score at weeks 4, 12 and 26

	Aripiprazole 10 mg			Aripiprazole 30 mg			Placebo		
	N	Baseline*	Mean change from baseline	N	Baseline*	Mean change from baseline	N	Baseline*	Mean change from baseline
Week 4	19	21.11	-4.16	22	17.59	-2.09	29	24.48	-13.62
Week 12	12	22.83	-8.33	13	15.38	-4.85	20	24.95	-15.50
Week 26	7	26.14	-7.17	8	16.50	-2.25	19	24.47	-16.84

* Baseline = Last evaluation from parent study 31-03-240
Source: CT-5.2 of Clinical Study Report 31-03-241

Other efficacy endpoint results, described as mean change from baseline to week 26, are summarized in Table 10.

Table 10 Other efficacy results at week 26

	Aripiprazole 10 mg			Aripiprazole 30 mg			Placebo		
	N	Baseline*	Mean change from baseline	N	Baseline*	Mean change from baseline	N	Baseline*	Mean change from baseline
CGI-BP Severity – Mania[a]	7	3.71	-0.86	8	2.38	-0.13	19	4.00	-1.94
CGI Severity – Depression[a]	7	1.86	-0.43	8	2.00	0.00	19	2.42	-0.79
CGI Severity – Overall Bipolar Illness[a]	7	3.71	-0.71	8	2.88	-0.63	19	4.95	-2.05
GBI Total Parent/Guardian Version – Mania[a]	7	9.71	-5.00	8	10.25	-3.25	18	14.22	-8.72

	Aripiprazole 10 mg			Aripiprazole 30 mg			Placebo		
	N	Baseline*	Mean change from baseline	N	Baseline*	Mean change from baseline	N	Baseline*	Mean change from baseline
GBI Total Subject Version – Mania[a]	7	8.71	-2.00	8	8.28	-1.38	19	9.16	-4.47
GBI Total Parent/Guardian Version – Depression[a]	7	8.29	-2.00	8	8.88	-2.13	18	9.39	-3.67
GBI Total Subject Version – Depression[a]	7	6.29	-1.82	8	9.75	-4.63	19	7.32	-2.95
ADHD-RS-IV Total[a]	6	27.50	-4.83	9	25.00	-0.75	18	31.83	-15.61
P-QLES-Q Total[b]	7	48.57	0.29	8	52.88	0.63	18	69.00	4.28

* Baseline = Last evaluation from parent study 31-03-240
[a] A negative mean change from baseline indicates improvement
[b] A positive mean change from indicates improvement
Source: CT-5.2 and CT-5.3 of Clinical Study Report 31-03-241

1.3.2.3. Ancillary analyses

At the CHMP request, comparative data up to 12 weeks were provided by the MAH to further support the maintenance of the effect. The MAH presented these data for lower and higher age groups (10-12 and 13-17 years old) since the MAH proposed to revise the indication applied for from 10-17 years old to 13-17 years old due to the CHMP concerns over the safety profile in the younger population (see 2.3.3).

In addition, subgroup analyses were also provided to evaluate the efficacy in patients with or without comorbidities including the effect on symptoms specific to mania in these population subgroups. Patients characteristics from 2 publications were presented to address the CHMP concern over the generalisibility of the pivotal study results (31-03-240) to the EU population since it included only US patients.

Maintenance of the effect

Efficacy Results are presented in Tables 11- 13.

Table 11

Table 1-2: Mean Change of YMRS Score from Baseline by Age Group

Visit/week	10 – 12 years						13 – 17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
OC												
Baseline	31	31.5	40	28.4	36	29.9	65	29.0	59	30.3	58	31.9
Week 4	25	-16.0**	30	-15.5**	26	-5.8	53	-14.9*	45	-17.9*	41	-11.1
Week 12	17	-20.4	17	-20.6	7	-15.8	34	-21.4	25	-20.5	13	-21.5
LOCF												
Baseline	31	31.5	40	28.4	36	29.9	65	29.0	59	30.3	58	31.9
Week 4	31	-15.6**	40	-15.5**	34	-4.7	65	-13.9*	59	-16.8**	58	-10.1
Week 12	31	-16.2**	40	-15.9**	36	-6.9	65	-15.6*	59	-16.8**	58	-9.7
* p < 0.05, ** p < 0.001 vs. Placebo												

[a] LS = Least Squares
a negative mean indicates improvement

Table 12

Table 1-3: Mean Change from Baseline by age group for CGI-BP Severity Score for Mania

Visit/week	10 – 12 years						13 – 17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
OC												
Baseline	31	4.8	40	4.6	36	4.7	65	4.6	59	4.6	58	4.9
Week 4	25	-1.6*	30	-2.0**	26	-0.7	53	-1.9*	45	-2.2**	41	-1.1
Week 12	17	-2.1	17	-2.8	7	-2.2	34	-2.7	25	-2.8	13	-2.5
LOCF												
Baseline	31	4.8	40	4.6	36	4.7	65	4.6	59	4.6	58	4.9
Week 4	31	-1.6*	40	-2.0**	34	-0.5	65	-1.7*	59	-2.1**	58	-1.0
Week 12	31	-1.6*	40	-2.2**	36	-0.9	65	-1.9*	59	-2.2**	58	-1.1
* p < 0.05, ** p < 0.001 vs. Placebo												

[a] a negative mean indicates improvement

Table 13

Table 1-4: Mean Change of CDRS-R Score from Baseline by Age Group

Visit/week	10 – 12 years						13 – 17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
OC												
Baseline	31	33.5	38	33.1	31	33.1	60	36.1	56	34.8	55	34.2
Week 4	25	-7.3	29	-7.3	23	-5.0	50	-8.2	42	-6.3	40	-6.7
Week 12	17	-9.1	16	-5.4	6	-14.3	31	-11.0	23	-8.9	13	-12.9
LOCF												
Baseline	31	33.5	38	33.1	31	33.1	60	36.1	56	34.8	55	34.2
Week 4	31	-7.3	38	-5.4	30	-4.1	60	-7.8	56	-6.4	55	-5.0
Week 12	31	-7.6	38	-5.0	31	-5.4	60	-8.1	56	-5.6	55	-4.8
* p < 0.05, ** p < 0.001 vs. Placebo												

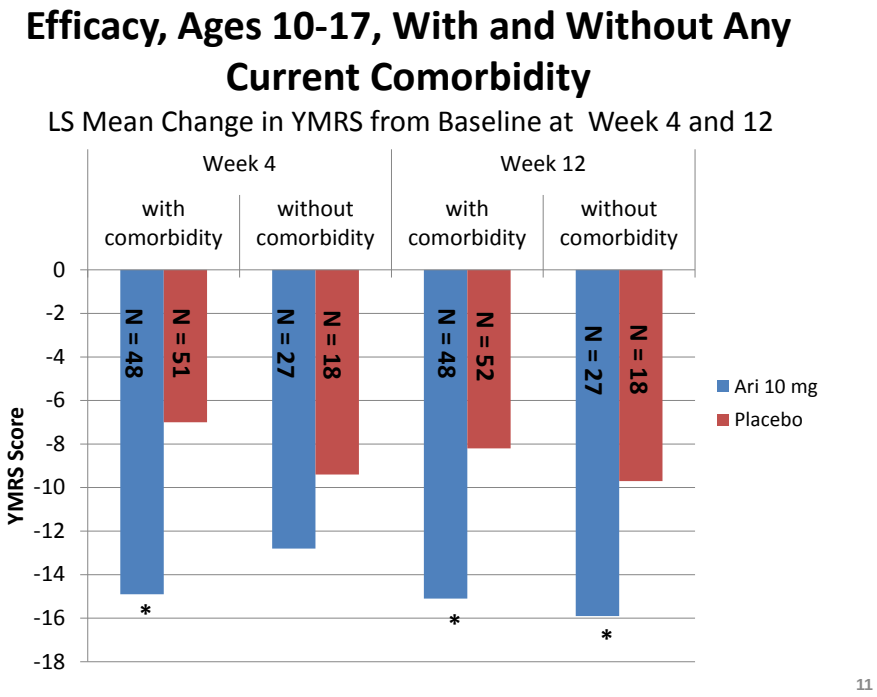
[a] a negative mean indicates improvement

At week 12, approximately half of the subjects receiving aripiprazole remained in the double-blind study, compared with about one quarter of subjects receiving placebo. Of the 77 subjects on placebo who left the double-blind study by week 12, over half of them (n = 42, 54.5%) left because of lack of efficacy. In contrast, of the 103 subjects receiving aripiprazole who discontinued by week 12, only 23 (22.3%) left because of lack of efficacy.

Efficacy in patients with or without comorbidities

The analysed subgroups (patients with or without any psychiatric comorbidity, with or without ODD, with or without ADHD) were of small sizes to provide a robust statistical analysis. Results indicated that the presence of any psychiatric comorbidity did not seem to influence the YMRS changes at weeks 4 and 12 (see Figure 3), this being less evident with patients with or without ADHD at both week 4 and 12 for the 30 mg dose. According to the MAH, the smaller effect observed in patients without ADHD versus patients with ADHD could be explained by a stronger placebo response obtained in the patients without ADHD as compared to patients with ADHD. To further address this point, a new subgroup analysis was performed by the MAH including "ongoing ADHD" instead of "ADHD" with the aim of evaluating whether this would lead to an effect on the total YMRS (see Tables 14-17, Figure 4).

Figure 3



Efficacy in patients with or without ADHD

Table 14

Table 1-1: Number of Patients with or Without Current Comorbid ADHD Separated by Age Group

	10 – 12 years	13 – 14 years	15 – 17 years	Total (10 – 17 years)
Patients with current comorbid ADHD	67	33	39	139
Patients without current comorbid ADHD	22	30	40	92

Table 15

Table 1-2: Patients with and Without Current ADHD: Mean Change from Baseline by Age Groups 10-17 and 13-17 for YMRS Total Score (LOCF)

Visit/ Week	10 – 17 years (N=231)						13 – 17 years (N=142)					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
Current ADHD												
Week 4	44	-15.17**	48	-15.90**	46	-6.327	23	-15.06*	23	-16.20*	26	-9.55
Week 12	44	-15.56**	48	-16.66**	47	-7.01	23	-16.95*	23	-17.08*	26	-8.32
No ADHD												
Week 4	37	-12.71	30	-14.59*	25	-9.88	31	-12.54	22	-14.16	17	-10.88
Week 12	37	-15.72*	30	-13.44	25	-9.96	31	-15.45	22	-12.55	17	-10.58
* p < 0.05, ** p < 0.001 vs. Placebo												

[a] Derived from ANCOVA model with terms of treatment as factor and baseline value as covariate (a negative mean indicates improvement).

Table 16

Table 1-3: Patients with and Without Current ADHD: Mean Change from Baseline by Age Group 10-12, 13-14, and 15-17 for YMRS Total Score (LOCF)

Visit/ Week	10 – 12 years (N=89)						13 – 14 years (N=63)						15 – 17 years (N=79)					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
Current ADHD																		
Week 4	21	-15.32**	25	-15.51**	20	-2.28	7	-12.63	11	-17.57*	15	-9.43	16	-16.14	12	-15.15	11	-9.46
Week 12	21	-13.95*	25	-16.27**	21	-5.48	7	-15.61	11	-18.39*	15	-7.50	16	-17.55	12	-16.15	11	-9.13
No ADHD																		
Week 4	6	-14.96	8	-15.11*	8	-7.42	15	-12.55	7	-12.84	8	-9.74	16	-12.34	15	-14.80	9	-12.17
Week 12	6	-16.67*	8	-16.23*	8	-8.64	15	-14.98	7	-13.00	8	-8.16	16	-15.84	15	-12.32	9	-12.86
* p < 0.05, ** p < 0.001 vs. Placebo																		

[a] Derived from ANCOVA model with terms of treatment as factor and baseline value as covariate (a negative mean indicates improvement).

Table 17

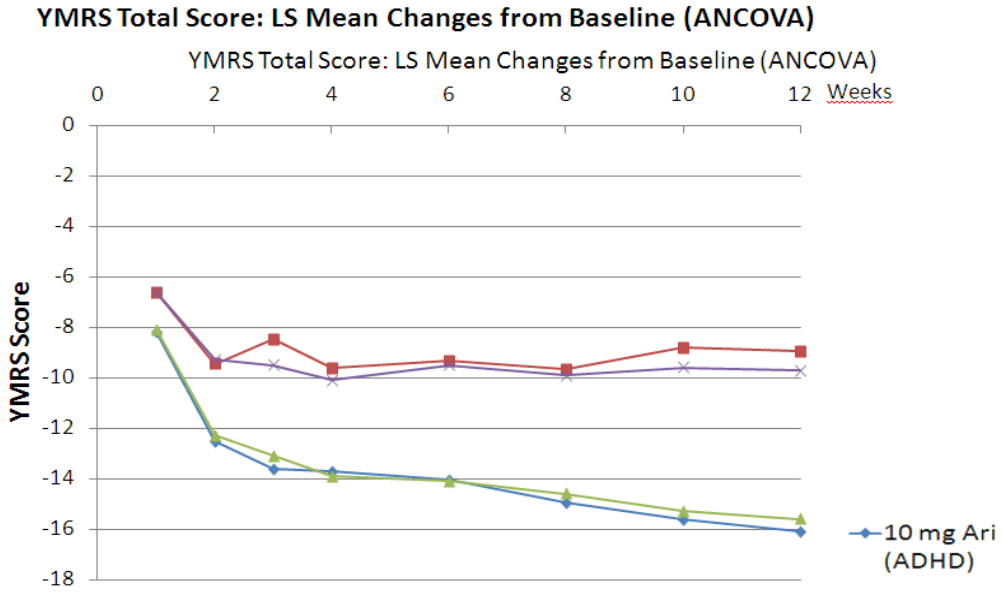
Table 1-4: Summary of the ANCOVA Analyses Focusing on the Effect of Aripiprazole and ADHD (p-values Presented for Effect of Model Variables)

		ARI 10 mg			ARI 30 mg		
New Model:[a] Variables: Aripiprazole, ADHD, Baseline YMRS Total Score							
Age Group	**Week**	**ARI 10 mg**	**ADHD**	**Baseline YMRS**	**ARI 30 mg**	**ADHD**	**Baseline YMRS**
10-17	4	<0.0001	0.46	<0.0001	<0.0001	0.36	0.0016
	12	<0.0001	0.17	<0.0001	<0.0001	0.94	0.0038
13-17	4	0.037	0.98	0.0010	0.0067	0.70	0.0081
	12	0.0015	0.63	0.0050	0.0081	0.91	0.028
Original Model:[b] Variables: Aripiprazole, Baseline YMRS Total Score							
Age Group	**Week**	**ARI 10 mg**	**ADHD**	**Baseline YMRS**	**ARI 30 mg**	**ADHD**	**Baseline YMRS**
10-17	4	<0.0001	-	<0.0001	<0.0001	-	<0.0001
	12	<0.0001	-	<0.0001	<0.0001	-	<0.0001
13-17	4	0.0234	-	<0.0001	<0.0001	-	<0.0001
	12	0.0012	-	<0.0001	0.0001	-	<0.0001

[a] New Model = ANCOVA model with terms of treatment and ADHD as factors and baseline value as covariate. P-values for ARI 10 mg or ARI 30 mg were derived from ANCOVA model.

[b] Original Model = ANCOVA model with terms of treatment as factor and baseline value as covariate (specified model for primary analysis). P-values for ARI 10 mg and ARI 30 mg were derived from pair-wised comparision within ANCOVA model. P-values for baseline YMRS total score were derived from ANCOVA model for covariate.

Figure 4



* p <0.05 for ARI 10 mg from week 2-12 adjusting only for baseline YMRS

* p <0.05 for ARI 10 mg from week 3-12 when adjusting also for ADHD

Generalisability of the efficacy results from study 31-03-240

Characteristics of EU population versus US population are presented in Table 18.

Table 18

Table 2-26: Patient Characteristics in European Studies Compared to Study 31-03-240

Clinical characteristics	Soutullo *et al.* (SPAIN) N = 38	Masi *et al.* (ITALY) N = 98	Study 31-03-240 (US) N = 297
Age at time of study	n/a[a]	13.7	13.4
Percent male	79	58	54/46
Percent Caucasian	92	n/a	65
CGI-S	n/a	5.4	4.6 – 4.9[b]
Age of onset (years)	11.6	10.0	12.1
Percent with first degree relative with a psychiatric disorder[c]	76	n/a	44
Any Psychiatric Comorbidity	92.1%	76.2%	65.5%
ADHD	21.1%	37.8%	51.7%
ODD/CD[d]	15.8%	46.9%	31.4%/6.1%
Generalized Anxiety Disorder	15.8%[e]	37.7%	7.4%
Separation Anxiety	Not reported	22.4%	5.1%
Simple Phobia	Not reported	9.2%	3.0%
Panic Disorder	Not reported	16.3%	< 5%
Social Phobia	Not reported	25.5	< 5%

a. n/a: not available
b. depending on treatment arm
c. In 31-03-240, "family history of bipolar disorder"
d. ODD and CD were combined in the EU studies and are presented separately for the US study
e. "Anxiety" was specified in the Spanish study

1.3.2.4. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal 31-03-240 study had a single primary efficacy endpoint in acute phase: the mean change from baseline to week 4 in the YMRS total score. Bipolar disorders in children and adolescents are being increasingly reported and the need for adequate diagnosis and treatment is important, particularly since most prescribed treatments are based in small studies and there is a lack of authorised treatment for this disorder. The MAH developed a training and certification program ensuring that it would be rigorously applied. For a rater to be considered certified on the YMRS, they were first prequalified using a rater experience survey and then were required to successfully complete the didactic training and certification process. All raters were required to demonstrate inter-rater reliability before rating subjects in this trial. Furthermore, two "recalibration" ratings had to be performed at 6- and 12- month intervals after initial rater certification.

YMRS total score has been considered as a valid instrument to assess bipolar disorders and has been used in clinical practice since its development in 1978, including paediatric population (*J Am Acad Child Adolesc Psychiatry. 2002 Nov;41(11):1350-9. Discriminative validity of a parent version of the Young*

Mania Rating Scale. Gracious BL, Youngstrom EA, Findling RL, Calabrese JR.). A definition of clinically significant mean value difference of YMRS total score has not been pre-specified in the study design. Only responder definition was settled a priori and this was considered acceptable by the CHMP.

The study was conducted in 59 centres in the US. Demographic characteristics of the population may be significantly different from European population, both physical, psychological and cultural. Given the difference of opinion between the US and the EU about the diagnosis and treatment of bipolar disorder in children and adolescents, and the discrepancies reported in the literature in terms of disease on-set between US and EU bipolar I patient populations, the validity of extrapolating the results of the US-based studies to the EU population was questioned by the CHMP. Data on 2 EU studies conducted in Spain and Italy in patients with Bipolar I disorder however showed similar patients characteristics regarding severity of illness and age of onset (see Table 18). Differences were noted on the presence of any psychiatric comorbidity with even lower rates of comorbidities in the US patients, although the ADHD diagnosis was more frequently observed in study 31-03-240 with 51.7% versus 21.1% and 37.8%, respectively, in Spain and Italy. Bipolar I disorder population is more prone to co-morbidities than schizophrenic population, and overall the CHMP considered that these data were sufficiently supporting the extrapolation of study 31-03-240 to the intended European population.

The study was a double blind placebo controlled consisting of an acute 4 week phase and a 26 week maintenance phase. The duration of the study was therefore longer than the recommended 12 week maintenance trial as referred in the "Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Bipolar Disorder", (CPMP/EWP/567/98).

Efficacy data and additional analyses

In the acute phase, treatment with aripiprazole resulted in statistically significant improvements (LOCF) compared with placebo in the primary efficacy endpoint YMRS Total Score at week 4 in both 10 mg (-5.99, CI:-8.49;-3.50, p<0.0001) and 30 mg (-8.26, CI:-10.7;-5.77, p<0.0001).

This efficacy was maintained through week 30 showing a statistically significant sustained improvement over placebo in both 10 mg (-5.89, CI:-8.70;-3.08, p<0.0001) and 30 mg (-6.73, CI:-9.53;-3.94, p<0.0001). Mean changes in YMRS Total Scores at week 30 using LOCF data were −14.1 in the aripiprazole 10 mg arm, −14.9 in the aripiprazole 30 mg arm, and −8.2 in the placebo arm.

Significant improvements were also documented for the secondary efficacy endpoints: CGAS, CGI-BP Severity Score for mania and for overall bipolar illness, GBI Total Score for mania and for the ADHD rating scale. For efficacy endpoints evaluating the effect of treatment on depressive symptoms (CGI-BP Severity Score for depression, GBI Total Score for depression and CDRS) no statistically significant superiority of aripiprazole over placebo treatment was observed.

Both the aripiprazole 10 mg and 30 mg arms had significantly higher percentages of responders compared to the placebo arm at every treatment week during both at week 4 and and at week 30 using the LOCF data set, thus showing maintenance of the effect of treatment. At week 4, percentages of responders were 44.79 % and 63.64% for 10 and 30 mg group as compared to 26.09% for the placebo group. At week 30, percentages of responders were around 50% and 55.56% for 10 and 30 mg group as compared to 26.6% for the placebo group

In study 31-03-240, the placebo effect was always high and particularly significant in the acute phase, but it did not reduce with time in the double blind extension phase. In addition, the number of patients who completed the 26 week extension phase was low: 34, 22 and 12 patients respectively in the

10 mg , 30 mg doses of aripiprazole and placebo groups. During the oral explanation, the MAH presented further analysis of the drop out rates showing that discontinuation with aripiprazole 10 mg due to lack of efficacy or lack of tolerability was low [at week 4: 2 (3%); at week 12: 11 (16.7%)] and more frequent with placebo [at week 4: 4 (6.7%); at week 12: 26 (43%)]. Among the drop outs occurring between week 4 and week 12, half of the patients treated with aripiprazole 10 mg went into the open label study and all of them were completers at week 12 as compared to 70% of patients treated with placebo and 85.7% of them were completers at week 12. It was also noted that discontinuation rates were of similar magnitude of studies conducted in adults with Bipolar I disorder.

An analysis of the time to discontinuation due to all reasons revealed that statistically significant differences were noted between both the aripiprazole 10 mg arm versus placebo ($p < 0.0001$) and 30 mg arm versus placebo ($p = 0.0124$). For both aripiprazole doses, the proportions of subjects remaining in the study (as measured by the Kaplan-Meier curve) were superior to that of placebo. The median times that subjects remained in the study were 109 days for the aripiprazole 10 mg arm, 66 days for the aripiprazole 30 mg arm, and 37 days for the placebo arm. With regard to time to discontinuation for all reasons, both aripiprazole doses showed statistically significantly superior retention profiles over the 30-week study (in Kaplan-Meier curves), i.e., proportions of subjects remaining in the study at different time points, compared to placebo.

At the CHMP request, subgroup analyses on efficacy for patients aged 13-14 years versus 15-17 years were performed as the proposed choice to restrict the age to 13-17 years due to safety concerns (see 2.3.3) was not based on clinical milestones. However, these data did not show any differences on the positive trends of improvement on YRMS and CGI-BP scores. The CHMP also acknowledged that further interpretation of such analysis is limited in the absence of statistical power.

Efficacy in patients with and without comorbidities

Following the CHMP concern over the patient population included in the study 31-03-240 (mixing Bipolar I disorder with other comorbidity conditions), a number of post-hoc analyses were performed by the MAH. Results showed that the population without comorbid disorders did not differ significantly in mean change of YMRS in both 10 mg aripiprazole and placebo by week 4 thus questioning as to whether aripiprazole may act mainly in symptoms common to ADHD / ODD and not specifically on Bipolar Disorder type I. Additional subgroup analyses however indicated that the presence of any comorbidity did not seem to influence the YMRS changes at weeks 4 and 12, this was being less evident with patients with or without ADHD at both weeks 4 and 12 for the 30 mg dose.

In a further subgroup analysis of patients with or without ADHD, the CHMP noted that the selected patients included “ongoing ADHD” instead of “ADHD” with the aim of evaluating whether this would lead to an effect on the total YMRS. Only “current comorbid ADHD” were selected: subjects with either a current diagnosis of ADHD or who discontinued medication for ADHD in the run-in phase were included in this definition. Previous ADHD comorbidity definition relied on the post hoc analysis of the Kiddie Schedule for Affective disorders, and had “unknown” values for 59 subjects. This new “current ADHD” definition was considered more inclusive by the CHMP and may therefore better reflect real ADHD comorbidity in this population. Almost half of patients with ADHD were included in the 10-12 years old group. Nevertheless, the effect of ADHD in the 13-17 years old group was still significant, with a difference of >2 points improvement (as compared to baseline) in the YMRS total score in patients with ADHD versus no ADHD, but placebo had also more pronounced improvement in the older patients (see Table 15). The trend towards better reduction of YMRS total score was present in all treatment groups and age ranges, despite the small sample in the subgroup analysis, both at 4 and 12

weeks. The CHMP further noted a very clear placebo effect increasing with age, both at weeks 4 and week 12, and the difference in response to placebo between ADHD and no ADHD patients was kept constant in the 3 different age groups (10-12, 13-14 and 15-17, Table 16). Therefore, the CHMP concluded that 15-17 age group had clearly a more pronounced placebo effect, rendering aripiprazole treatment effect less evident.

During the oral explanation, the MAH presented the data for the 10 mg dose showing same directional improvements on the YRMS score at weeks 4 and 12 (Figure 3) in patients with or without any comorbidities and the subgroup analysis showing that ADHD status did not change the 10 mg treatment effect significantly, particularly at week 12, where the use of ADHD medication was already permitted and favoured aripiprazole effect independently the presence of ADHD or ADHD medication (Figure 4).

Maintenance of the effect

At week 12, 53% and 42% of patients treated respectively with aripiprazole 10 mg and 30 mg were still receiving treatment. Mean changes in YMRS score in placebo, 10 mg and 30 mg were respectively -8.2, -15.7 and -16.5.

When compared to the placebo at week 12, the efficacy was maintained with a statistically significant differences over the placebo for both 10 mg and 30 mg on the YRMS score total score and in both analysed age groups. In the 10-12 years old group, mean changes in YMRS Total Scores at week 12 using LOCF data were: −16.2 in the aripiprazole 10 mg arm, −15.9 in the aripiprazole 30 mg arm, and −6.9 in the placebo arm using LOCF data (for both doses, $p<0.05$). In the 13-17 years old group, mean changes in YMRS Total Scores at week 12 using LOCF data were: −15.6 in the aripiprazole 10 mg arm, −16.8 in the aripiprazole 30 mg arm, and −9.7 in the placebo arm using LOCF data (for 10 mg: $p<0.05$, for 30 mg: $p<0.001$). Similar findings were obtained for the secondary endpoints using LOCF data. However, the OC analysis failed to show statistical significant over the placebo for both doses on all analysed efficacy endpoints for both age groups. Considering the number of discontinuation (77/99 patients), the CHMP considered that the OC analysis did not provide any relevant findings apart that a significant percentage of patients did improve spontaneously by week 12, suggesting that the treatment should not be prolong longer than 12 weeks. The CHMP was therefore of the opinion that the efficacy was demonstrated up to 12 weeks only and the treatment should be therefore limited to this duration.

Having considered the written responses and oral explanation given by the MAH, the CHMP considered that the presented efficacy data were sufficiently supportive of an efficacy of aripiprazole on manic episodes in the paediatric Bipolar I disorder population.

Dosing recommendation

The MAH initially proposed to recommend 10 mg /day as aripiprazole dose for the treatment of paediatric subjects 10 to 17 years of age with bipolar I disorder. Treatment initiation was proposed to start at 2 mg titrated to 5 mg after 2 days and to the target dose of 10 mg after two additional days. When appropriate, subsequent dose increases should be administered in 5 mg increments. The maximum daily dose should not exceed 30 mg. Since 5 mg had been tested in schizophrenia and 10 mg were the lowest efficacious dose in adults, this was the lowest dose chosen. For the highest range the MAH choose the highest tolerated dose in trials CN138-014 and 31-03-238.

However, the CHMP considered that enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated when comparing results from the 10 mg and 30 mg groups (See Tables 5 and 6). In addition, taking into consideration the safety profile in this paediatric population, (see section 2.3.3), the use of the 30 mg dose was not recommended by the CHMP, and an increase over 10 mg should only be performed under strict surveillance. The CHMP recommended the following SmPC information regarding the posology in the paediatric Bipolar I disorder population:

"Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg.

The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant undesirable effects including EPS related events, somnolence, fatigue and weight gain (see section 4.8). Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring (see sections 4.4, 4.8 and 5.1).

Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, ABILIFY is not recommended for use in patients below 13 years of age (see sections 4.8 and 5.1)."

1.3.3. Clinical safety

The safety of aripiprazole in the treatment of bipolar I disorder in children and adolescents was evaluated in the two clinical studies that were already discussed in clinical efficacy: Study 31-03-240 and Study 31-03-241. No pooling with other clinical trials regarding children and adolescents with bipolar disorder was performed and the safety data presented below relates to both study 31-03-240 and 31-03-241.

1.3.3.1. Patient exposure

A total of 296 subjects with bipolar I disorder were enrolled in Study 31-03-240. Thereof, 86 subjects rolled over to the open-label Study 31-03-241. The total number of children and adolescents with bipolar I disorder exposed to aripiprazole in Study 31-03-240 and 31-03-241 was 233.

Of the 296 subjects randomized, a total of 197 subjects were exposed to aripiprazole: 98 in the 10 mg arm, with an average dose of 8.6 mg overall (8.3 mg in the acute Phase and 9.3 mg in the extension phase), and 99 in the 30 mg arm, with an average dose of 22.1 mg (19.5 in the acute phase and 27.5 in the extension phase). A total of 99 subjects were randomized to placebo (2 subjects from the placebo arm did not receive study drug). The percentages of subjects exposed to study medication beyond the planned 26-week double blind extension phase treatment period were 14.3%, 10.2%, and 5.1% in the aripiprazole 10 mg and 30 mg and the placebo arm, respectively.

Table 19 Patient exposure to aripiprazole or placebo by duration in study 31-03-240

Study Days	Aripiprazole 10 mg (N = 98)		Aripiprazole 30 mg (N = 99)		Placebo (N = 99)
	n (%)[a]	Average Dose (mg)	n (%)[a]	Average Dose (mg)	n (%)[a]
1 - 7 Days	98 (100)	6.0	99 (100.0)	6.9	97 (98.0)
8 - 14 Days	94 (95.9)	9.6	95 (96.0)	22.3	87 (87.9)
15 - 21 Days	85 (86.7)	9.4	81 (81.8)	28.5	80 (80.8)
22 - 28 Days	84 (85.7)	9.5	77 (77.8)	28.5	70 (70.7)
29 - 42 Days	81 (85.2)	9.4	69 (69.7)	27.1	65 (65.7)
43 - 56 Days	64 (65.3)	9.4	58 (58.6)	27.5	37 (37.4)
57 - 70 Days	58 (59.2)	9.4	51 (51.5)	28.2	30 (30.3)
71 - 84 Days	56 (57.1)	9.3	47 (47.5)	28.0	23 (23.2)
85 – 102	52 (53.1)	9.3	42 (42.4)	28.0	20 (20.2)
103 – 140	47 (48.0)	9.2	36 (36.4)	27.7	17 (17.2)
141 – 168	43 (43.9)	9.2	27 (27.3)	26.5	16 (16.2)
169 – 182	39 (39.8)	9.3	23 (23.2)	27.1	15 (15.2)
183 – 210	34 (34.7)	9.4	23 (23.2)	26.6	13 (13.1)
> 210	14 (14.3)	9.6	10 (10.1)	24.5	5 (5.1)
During Acute Phase	98 (100.0)	8.3	99 (100.0)	19.5	97 (98.0)
During Maintenance Phase	75 (76.5)	9.3	71 (71.7)	27.5	64 (64.6)
Overall during the study	98 (100.0)	8.6	99 (100.0)	22.1	97 (98.0)

a: Percentages are based on the number of randomized subjects who received at least one dose of study medication
Source: CSR 31-03-240, CT-7

Table 20 Exposure to aripiprazole by dose level in study 31-03-240

Treatment Duration[a]	Study 31-03-240, Subjects with Bipolar I Disorder (N=86)	
	n (%)[b]	Average daily dose (mg)
1 - 7 Days	3 (3.5)	4.9
8 - 14 Days	1 (1.2)	10.6
15 - 21 Days	0	--
22 - 28 Days	1 (1.2)	5.6
29 - 56 Days	11 (12.8)	14.3
57 - 84 Days	8 (9.3)	17.7
85 - 112 Days	8 (9.3)	17.7
113 - 140 Days	10 (11.6)	17.3
141 – 168 Days	9 (10.5)	14.3
169 – 181 Days	17 (19.8)	14.0
≥ 182 Days	18 (20.9)	15.9
Overall during the study[c]	86 (100)	15.1

a: Study medication end date – study medication start day + 1. Each subject is counted once in the highest possible category
b: Percentages were based on the number of enrolled subjects
c: including subjects who received at least one dose of study medication
Sources: Study 31-03-241, CT-7

1.3.3.2. Adverse events

Study 31-03-240

During the entire study period, a total of 376 TEAEs were experienced by 78/98 (79.6%) subjects in the aripiprazole 10 mg arm; 366 TEAEs were experienced by 84/99 (84.8%) subjects in the aripiprazole 30 mg arm; and 164 TEAEs were experienced by 64/97 (66.0%) subjects in the placebo arm.

The most common TEAEs reported at an incidence rate of ≥ 5% in the aripiprazole 10 mg arm were somnolence (24.5%), headache (20.4%), fatigue (18.4%), nausea (13.3%), vomiting (13.3%), extrapyramidal disorder (12.2%), vision blurred (10.2%), nasal congestion (10.2%), upper abdominal pain (9.2%), akathisia (9.2%), increased weight (8.2%), increased appetite (8.2%), upper respiratory tract infection (8.2%), decreased appetite (7.1%), nasopharyngitis (7.1%), cough (7.1%), dizziness (7.1%), insomnia (6.1%), back pain (5.1%), anxiety (5.1%), dysmenorrhea (5.1%), and pharyngolaryngeal pain (5.1%).

The most common TEAEs reported at an incidence rate of ≥ 5% in the aripiprazole 30 mg arm were extrapyramidal disorder (28.3%), somnolence (27.3%), headache (23.2%), nausea (14.1%), akathisia (13.1%), fatigue (12.1%), vomiting (8.1%), vision blurred (8.1%), increased appetite (8.1%), salivary hypersecretion (8.1%), upper respiratory tract infection (6.1%), stomach discomfort (6.1%), bipolar disorder (6.1%), upper abdominal pain (5.1%), increased weight (5.1%), dizziness (5.1%), diarrhoea (5.1%), and dystonia (5.1%). In the placebo arm during the entire study, the most common TEAEs were headache (18.6%), vomiting (9.3%), bipolar disorder (5.2%), and nausea (5.2%).

From the acute phase to the extension phase there did not appear to be any unexpected increases in the incidence of the most common TEAEs associated with aripiprazole.

Following CHMP concerns over the safety profile in Bipolar I disorder paediatric patients (younger than the authorised paediatric indication for schizophrenia), the MAH presented a comparison of the safety profile for 10-12 years and 13-17 years to support their proposal to revise the indication applied for from 10-17 years to 13-17 years. Overall AE profile is presented in Table 17. Other safety subgroup analyses (10-12 years versus 13-17 years) are presented under the relevant sections together with the other additional safety data requested by the CHMP comparing 13-14 years to 15-17 years (see EPS related symptoms, weight gain related events).

Table 21

Table 3-1: TEAEs ≥ 5% in Subjects 10 – 12 years versus 13 - 17 years (Week 12)

	10-12 years			13-17 years		
MedDRA Term	**Arip 10mg N = 32 n (%)**	**Arip 30mg N = 40 n (%)**	**Placebo N = 39 n (%)**	**Arip 10mg N = 66 n (%)**	**Arip 30mg N = 59 n (%)**	**Placebo N = 58 n (%)**
Vision blurred	2 (6.3)	4 (10.0)	0	7 (10.6)	4 (6.8)	0
Abdominal Pain upper	2 (6.3)	3 (7.5)	1 (2.6)	6 (9.1)	2 (3.4)	2 (3.4)
Diarrhoea	0	2 (5.0)	0	4 (6.1)	3 (5.1)	0
Nausea	5 (15.6)	6 (15.0)	0	8 (12.1)	8 (13.6)	5 (8.6)
Salivary Hypersecretion	1 (3.1)	3 (7.5)	0	2 (3.0)	5 (8.5)	0
Stomach discomfort	1 (3.1)	2 (5.0)	2 (5.1)	1 (1.5)	4 (6.8)	0
Vomiting	5 (15.6)	4 (10.0)	3 (7.7)	7 (10.6)	4 (6.8)	6 (10.3)
Fatigue	4 (12.5)	3 (7.5)	2 (5.1)	12 (18.2)	8 (13.6)	2 (3.4)
Pyrexia	2 (6.3)	2 (5.0)	0	-	-	-
Gastroenteritis viral	0	1 (2.5)	2 (5.1)	1 (1.5)	3 (5.1)	0
Influenza	0	0	2 (5.1)	-	-	-
Nasopharyngitis	4 (12.5)	1 (2.5)	1 (2.6)	-	-	-
Upper respiratory tract infection	2 (6.3)	2 (5.0)	1 (2.6)	3 (4.5)	1 (1.7)	2 (3.4)
Blood creatinine phosphokinase increased	-	-	-	1 (1.5)	4 (6.8)	0
Weight increased	2 (6.3)	3 (7.5)	0	5 (7.6)	2 (3.4)	1 (1.7)
Decreased appetite	1 (3.1)	3 (7.5)	0	6 (9.1)	1 (1.7)	3 (5.2)
Increased appetite	2 (6.3)	4 (10.0)	1 (2.6)	3 (4.5)	3 (5.1)	2 (3.4)
Arthralgia	1 (3.1)	2 (5.0)	0	-	-	-
Neck pain	2 (6.3)	0	0	-	-	-
Pain in extremity	0	2 (5.0)	0	-	-	-
Akathisia	-	-	-	8 (12.1)	12 (20.3)	1 (1.7)
Dizziness	-	-	-	7 (10.6)	4 (6.8)	1 (1.7)
Dystonia	-	-	-	1 (1.5)	5 (8.5)	0
Extrapyramidal disorder	6 (18.8)	10 (25.0)	2 (5.1)	6 (9.1)	17 (28.8)	1 (1.7)
Headache	5 (15.6)	9 (22.5)	4 (10.3)	14 (21.2)	13 (22.0)	14 (24.1)
Lethargy	1 (3.1)	2 (5.0)	0	-	-	-
Sedation	2 (6.3)	0	0	-	-	-
Somnolence	5 (15.6)	11 (27.5)	0	19 (28.8)	16 (27.1)	3 (5.2)

Extrapyramidal Syndrome (EPS) related symptoms

The overall incidence of any extrapyramidal event was 25.8% (51/197 subjects) in the combined aripiprazole group (10 mg and 30 mg) and 5.1% (5/97 subjects) in the placebo group during the acute phase. The most commonly reported EPS-related symptoms were Parkinsonism events (21.8% and 4.1% in the aripiprazole and placebo groups, respectively, during the acute phase). Akathisia events occurred in 10.1% (20/197 subjects) of the combined aripiprazole group and 2.0% (2/97 subjects) of the placebo group during the acute phase. There was no notable increase in akathisia events following the acute phase (up to week 30). Over the entire study period, the incidence of any extrapyramidal events (excluding akathisia) was 36.3% (36/99 subjects) in the aripiprazole 30 mg arm, 20.4% (20/98 subjects) in the 10 mg arm, and 5.1% (3/97 subjects) in the placebo arm.

In study 31-03-240, the overall rate of EPS symptoms (including akathisia) was 34.5 %, salivary hypersecretion and drooling were observed in 6% of the subjects.

EPS-SAS (SAS: Simpson Angus Scale) and EPS-AIMS (AIM:Abnormal Involuntary Movement Scale Scale) mean changes are presented for 10-12 years and 13-17 years groups in Tables 22 and 23.

Table 22

Table 3-11: EPS-SAS, Mean Changes from Baseline by Age Group

Visit/week	10 – 12 years						13 – 17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
OC												
Baseline	30	10.1	40	10.3	36	10.2	65	10.2	59	10.3	58	10.2
Week 4	24	1.0	30	1.8*	26	-0.2	53	0.3	45	1.0*	41	-0.0
Week 12	16	-0.3	17	0.6	7	-0.2	34	0.2	25	0.3	13	-0.1
LOCF												
Baseline	30	10.1	40	10.3	36	10.2	65	10.2	59	10.3	58	10.2
Week 4	30	1.3	40	1.6*	34	-0.1	65	0.2	59	0.9**	58	-0.1
Week 12	30	0.1	40	1.1*	36	-0.0	65	0.2	59	0.7*	58	-0.1
* p < 0.05, ** p < 0.001 vs. Placebo												

[a] a negative mean indicates improvement

Table 23

Table 3-13: EPS-AIMS, Mean Changes from Baseline by Age Group

Visit/week	10 – 12 years						13 – 17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
OC												
Baseline	31	0.0	40	0.1	36	0.1	65	0.1	59	0.0	58	0.2
Week 4	25	-0.1	30	-0.1	26	-0.1	53	-0.0	45	0.1	41	-0.0
Week 12	17	0.0	17	0.0	7	0.0	34	-0.1	25	-0.1	13	-0.1
LOCF												
Baseline	31	0.0	40	0.1	36	0.1	65	0.1	59	0.0	58	0.2
Week 4	31	-0.1	40	-0.1	34	0.1	65	-0.0	59	0.1	58	0.0
Week 12	31	-0.1	40	-0.1	36	0.0	65	-0.1*	59	-0.1	58	0.0
* p < 0.05, ** p < 0.001 vs. Placebo												

When comparing 13-14 and 15-17 age groups, akathisia was the most significant AE: 4 patients in the 13-14 years old group (but all resolved by week 12) and 4 patients in the 15-17 years old group (one led to discontinuation). Dystonia was not reported in the 13-14 years old group, while there was one case in the 15-17 years old group. There were 2 patients experiencing Parkinsonian symptoms in the 13-14 year old group, one led to drug discontinuation and another resolved by week 12; in the 15-17 years old group there were 4 reports of Parkinsonism, both resolved by week 12.

Seizures related events

One subject experienced a grand mal convulsion in the aripiprazole 10 mg arm during the acute phase. No other TEAEs related to seizures occurred.

Suicide related events

Two subjects experienced suicidal ideation, 1/98 (1%) in the aripiprazole 10 mg and 1/99 (1%) in the 30 mg arm in the acute phase of the study.

Intentional self-injury related events

Intentional self-injury was reported in 2/98 (2.0%) in the aripiprazole 10 mg arm, in 1/99 (1.0%) in the 30 mg arm, and in 1/97 (1.0%) in the placebo arm during the acute phase. Self mutilation was reported in 1/98 (1%) in the aripiprazole 10 mg and 1/99 (1%) in the 30 mg arm.

Weigth gain related events

There were no significant differences in weight change between aripiprazole and placebo in the end of the acute phase (at week 4).

The mean changes in weight at week 4 were 0.82, 1.08, and 0.56 kg for the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.3488$ and $p = 0.1276$ for the 10 mg and 30 mg arms, respectively, versus placebo). Mean changes from baseline in weight were significantly greater in the aripiprazole 10 mg and 30 mg arms versus placebo at week 12 through week 30 and at the last visit. The mean changes in weight at the end of the study (Last Visit) were 3.20, 2.85, and 0.98 kg for the aripiprazole 10 mg, 30 mg, and placebo arms, respectively ($p = 0.0002$ and $p = 0.0019$ for the 10 mg and 30 mg arms, respectively, versus placebo).

The percentages of subjects who experienced a potentially clinically significant weight gain (≥ 7% weight gain compared to baseline) at their Last Visit were 35.8% (34/95 subjects) in the aripiprazole 10 mg arm, 29.2% (28/96 subjects) in the aripiprazole 30 mg arm, and 9.8% (9/92 subjects) in the placebo arm. The differences from placebo in the incidence of potentially clinically significant weight gain were statistically significant at the Last Visit for both the aripiprazole 10 mg arm and 30 mg arm ($p < 0.0001$ and $p = 0.0009$, respectively), at week 30 for the 10 mg arm ($p=0.0487$), and at week 16 for the 30 mg arm ($p = 0.0337$).

At baseline 25.5%, 25.3%, and 21.6% in the aripiprazole 10 mg arm, aripiprazole 30 mg arm, and placebo arm, respectively, had a weight z -score ≥ 95th percentile. This proportion of subjects increased to 27.4%, 29.2%, and 22.8% in the aripiprazole 10 mg arm, aripiprazole 30 mg arm, and placebo arm, respectively, at the Last Visit. It was noted that a few subjects had shifts in weight z-scores from normal at baseline to abnormal at the last visit: 4 subjects in the aripiprazole 10 mg arm, 5 subjects in the aripiprazole 30 mg arm, and 2 subjects in the placebo arm.

Mean weight and BMI changes are presented for 10-12 years and 13-17 years groups in Tables 24 and 25.

Table 24

Table 3-4: Mean Weight Change (in kg) from Baseline by Age Group

Visit/week	10 – 12 years						13 – 17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	mean	N	mean	N	mean	N	mean	N	mean	N	mean
OC												
Baseline	32		40		39		66		59		58	
Week 4	26	1.2	31	1.4*	26	0.4	49	0.6	42	0.9	39	0.7
Week 12	16	2.8	16	4.0*	7	0.8	33	2.6*	25	2.1	14	0.2
LOCF												
Baseline	32		40		39		66		59		58	
Week 4	30	0.9	39	1.2	37	0.3	65	0.4	57	0.7	55	0.7
Week 12	30	2.2*	39	2.6**	37	0.4	65	1.6*	57	1.3	55	0.5
* $p < 0.05$, ** $p < 0.001$ vs. Placebo (Aripiprazole 10mg and Aripiprazole 30 mg treatment group)												

Table 25

Table 3-5: Body Mass Index (kg/m2), Mean Changes from Baseline by Age Group

Visit/week	10 – 12 years						13 – 17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	mean	N	mean	N	mean	N	mean	N	mean	N	mean
OC												
Baseline	32		40		39		66		59		58	
Week 4	26	0.5	30	0.5*	26	0.0	49	0.1	42	0.2	39	0.2
Week 12	16	0.9	16	1.4*	7	0.0	33	0.8*	25	0.4	14	0.0
LOCF												
Baseline	32		40		39		66		59		58	
Week4	30	0.3	38	0.5*	37	-0.0	65	0.0	57	0.1	55	0.2
Week 12	30	0.7*	38	0.9**	37	0.0	65	0.4	57	0.3	55	0.1
* $p < 0.05$, ** $p < 0.001$ vs. Placebo (Aripiprazole 10mg, and Aripiprazole 30 mg treatment group)												

When comparing 13-14 and 15-17 age groups, mean weight changes were significant with aripiprazole 10 mg in both age groups by week 12. In the OC analysis, increase weight of 2.7 Kg (placebo: 1.4 Kg) by week 12 in the 13-14 years old group versus 2.5 Kg (placebo 1.1 Kg) in the 15-17 years old group. Similar results were obtained using LOCF analysis. BMI index followed the same pattern.

Study 31-03-241.

A total of 214 TEAEs were experienced by 65/86 (75.6%) of subjects with bipolar I disorder in Study 31-03-241. The majority of TEAEs were mild or moderate in severity. 6/86 (7.0%) of subjects experienced SAEs.

The most commonly reported TEAEs by 5 % or greater incidence included: diarrhoea (5.8%), nausea (10.5%), Irritability (5.8%), upper respiratory tract infection (8.1%), weight increased (7.0%), akathisia (8.1%), dizziness (7.0%), headache (16.3%), somnolence (10.5%), nasal congestion (5.8%).

Extrapyramidal Syndrome (EPS) related symptoms

Parkinsonism were reported for 6/86 (6.9%) children and adolescents with bipolar I disorder in Study 31-03-241. Akathisia were reported for 7/86 subjects (8.1%). The majority of EPS-related AEs were mild to moderate in severity. None of the EPS-related AEs led to discontinuation. On subject reported dystona (1.1%).

Seizures related events

No seizures were reported in study 31-03-241.

Suicide related events

No cases of suicide ideation were reported in study 31-03-241 for subjects with bipolar I disorder.

Intentional self injury related events

In two out of eighty-six subjects (2.3%), intentional self-injury was reported as TEAE.

Weigth gain related events

At the Last Visit, the percentage of subjects who experienced a potentially clinically significant weight gain (≥ 7% compared to baseline) was 36/86 (44.2%).

Somnolence related events

At week 12, the incidence of somnolence was 20.0% and 34.1% in subjects 13-14 and 15-17 years, respectively, after treatment with aripiprazole 10 mg, compared to an incidence of 6.5% and 3.7%, respectively, after treatment with placebo. Sedation was not reported for any of the patients treated with aripiprazole 10 mg or placebo in subjects 13-14 and 15-17 years of age.

1.3.3.3. Serious adverse events and deaths

No deaths were reported in studies 31-03-240 and 31-03-241.

Study 31-03-240

A total of 18/294 (6.1%) subjects with Bipolar I disorder experienced SAEs.

The most commonly reported SAEs during the entire study were bipolar disorder (9/294 subjects; 3.1% overall) and bipolar I disorder (3/294 subjects, 1.0% overall). During the acute phase, bipolar disorder was reported as serious in 2 subjects (2.0%) of the aripiprazole 30 mg arm and in 4 subjects (4.1%) of the placebo arm. An additional 3 subjects in the aripiprazole 30 mg arm (for a total 5.1% in that group for the entire study) had SAEs of bipolar disorder after week 4. An SAE of bipolar I disorder was also reported in 2 subjects in the aripiprazole 30 mg arm after week 4, and 1 subject in the placebo arm during the acute Phase.

Other SAEs reported during the acute phase were fatigue (1 subject in the 10 mg arm), accidental overdose (1 subject in the 10 mg arm), grand mal convulsion (1 subject in the 10 mg arm), aggression (2 subjects in the 10 mg arm), oppositional defiant disorder (1 subject in the aripiprazole 10 mg arm), suicidal ideation (1 subject in the 10 mg arm), and respiratory arrest (1 subject in the 10 mg arm). Additional SAEs that were reported after week 4 were: increased libido (1 subject in the 30 mg arm) and mania (1 subject in the placebo arm).

Overall, 6 subjects experienced SAEs resulting in discontinuation of study medication: in the aripiprazole 10 mg arm, 1 subject was discontinued due to suicidal ideation, and 1 subject was discontinued due to aggression and fatigue; in the aripiprazole 30 mg arm, 3 subjects were discontinued due to bipolar disorder; and in the placebo arm, 1 subject was discontinued due to bipolar I disorder.

No relevant differences on the SAE profile were observed between the age groups of 10-12 years versus 13-17 years.

Study 31-03-241

A total of 6/86 (7.0%) patients experienced SAEs. The majority of these SAEs were severe in intensity. The following SAEs were reported: aggression (n=2), bipolar disorder (n=3), depression (n=1), and intentional self-injury (n=1).

1.3.3.4. Laboratory, Vital and Physical findings

Although, CPK elevation was identified as potential significant laboratory changes, no clinically relevant changes were noted in enzyme or serum chemistry elevations or changes in hematology parameters.

In study 31-03-240, one of 98 (1.0%) subjects in the aripiprazole 10 mg arm showed glycolysated haemoglobin increased during the acute phase. None was reported in study 31-03-241. However, significant changes in prolactin levels were observed and further details are provided below.

No clinically meaningful changes in mean QT or QTc intervals, or other ECG abnormalities, were observed. In study 31-03-241, an ECG abnormality (abnormal ECG) was reported as TEAE in one subject. This TEAE was not an SAE nor did it result in a discontinuation of study medication.

In both studies, pyrexia was reported: 3 subjects in the aripiprazole 10 mg and 4 subjects in the 30 mg arm in study 31-03-240 and 4/86 (437%) subjects in study 31-03-241. In addition significant orthostatic changes were noted. These were defined as a decrease of at least 20 mmHg in systolic blood pressure accompanied by an increase in heart rate of at least 25 bpm when changing from a supine to a standing position: 2 subjects in the aripiprazole 10 mg arm and 2 subjects in the placebo arm, corresponding to an incidence 2.1%, 0.0%, and 2.1% in the aripiprazole 10 mg arm, the aripiprazole 30 mg arm, and the placebo arm, respectively in study 31-03-240 and 5/86 (5.8%) subjects in study 31-03-241.

Prolactin levels

Study 31-03-240

Mean decreases in prolactin levels relative to baseline were observed in the two aripiprazole treatment arms in male subjects, and in both of the aripiprazole arms and the placebo arm in female subjects. The mean changes from baseline to the last visit in prolactin levels(in ng/ml) were −2.58, −3.39, and 0.72 in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms, respectively, in male subjects.

The incidence of low prolactin levels (less than 3 ng/dL in females and less than 2 ng/dL in males) during the acute phase was greatest in the aripiprazole 30 mg arm (35/89, 39.3%), followed by the aripiprazole 10 mg arm (22/87, 25.3%), and then by the placebo arm (2/85, 2.4%). For males, the total incidence of low prolactin levels was 38/89 (38.8%) in the aripiprazole arms and 2/47 (4.3%) in the placebo arm. For females, the total incidence of low prolactin levels was 19/87 (21.8%) in the aripiprazole arms and 0/38 (0.0%) in the placebo arm. During the entire study period, the overall incidence of low prolactin levels was greatest in the aripiprazole 30 mg arm (41/92, 44.6%), followed by the aripiprazole 10 mg arm (34/93, 36.6%), and then by the placebo arm (2/86, 2.3%). A higher proportion of males experienced decreased prolactin levels than females in both dose groups. For males, the total incidence of low prolactin levels was 49/92 (53.3%) in the aripiprazole arms and 2/47 (4.3%) in the placebo arm. For females, the total incidence of low prolactin levels was 26/93 (28.0%) in the aripiprazole arms and 0/39 (0.0%) in the placebo arm. None of these events were reported as TEAEs or SAEs or resulted in discontinuation of study medication.

Study 31-03-241

A decrease in prolactin levels relative to baseline was observed in children and adolescents with bipolar I disorder. The mean changes from baseline to the last visit in prolactin levels (in ng/ml) were: -1.55 at week 8; -1.24 ng/ml at week 18; -0.74 at week 26 and -0.88 at the last visit. For females the decreases in prolactin levels were smaller than for males. The incidence of low prolactin levels was 38/83 (45.8%). For females, the incidence of low prolactin levels was 9/34 (26.5%), for males 29/49 (59.2%). None of these events were reported as TEAEs or SAEs or resulted in discontinuation of study medication.

1.3.3.5. Discontinuation due to AES

Study 31-03-240

During the acute phase, a total of 16/294 (5.4%) subjects discontinued study medication due to a TEAE: 6/98 (6.1%) in the aripiprazole 10 mg arm, 8/99 (8.1%) in the aripiprazole 30 mg arm, and 2/97 (2.1%) in the placebo arm. During the entire 30-week study, a total of 30/294 (10.2%) subjects discontinued study medication due to a TEAE: 9/98 (9.2%) in the aripiprazole 10 mg arm, 19/99 (19.2%) in the aripiprazole 30 mg arm, and 2/97 (2.1%) in the placebo arm.

No relevant differences on the rates of discontinuation due to AEs were observed between the age groups of 10-12 years versus 13-17 years.

Study 31-03-241

One out of Eighty six (1.2%) subjects with bipolar I disorder discontinued study medication due to a TEAE : auditory hallucination.

1.3.3.6. Post marketing experience

During the six-month period from 17 July 2010 through 16 January 2011, among files for which the age of the patient was reported, there were a total of 234 healthcare professional confirmed cases (221 initial and 13 follow up) of AEs occurring in patients 17 years of age or younger. Of these cases, 223 were spontaneous cases and 11 were derived from published literature. Furthermore, 73 cases were classified as serious. The most frequently reported events experienced in the paediatric population were Weight increased (26), Tardive dyskinesia (14), Dystonia (13), Akathisia (12), Dizziness (8), Somnolence (8), Tremor (7), Vomiting (7), Nausea (6), Drug ineffective (5), Extrapyramidal disorder (5), Muscle rigidity (5), Premature baby (5), Small for dates baby (5), Swollen tongue (5), and Vision blurred (5).

The MAH performed a supplementary search of the most common AEs from the CARES (BMS Corporate Adverse Events Reporting and Evaluation System) database, by August 7, 2012. The estimated worldwide postmarketing aripiprazole exposure for patients aged 0-17 years was 1,451,600 patients, most on the schizophrenia indication. There were 151 cases of somnolence or sedation (131 reports from healthcare professionals, 20 from published literature). Of these cases, 39 were considered serious. The events reported to be similar across different pediatric age groups. There were 217 cases that fell under “Weight increased”. Of these cases, 214 were spontaneous cases, and 3 were from published literature. Thirty of the 217 cases were considered serious. The 217 cases which met criteria for inclusion in this search described 94 males and 86 females (gender not provided in 37 cases). The nature of the reported events related to weight increased was similar across different pediatric age groups. There were 442 cases of “Dyskinesias and movement disorders” or “Parkinson’s disease and Parkinsonism” which included 444 events. Of these cases, 1 case was from a clinical trial, 409 were spontaneous cases, and 14 cases were from published literature. Ninety-two of the 442 cases were

considered serious. reported events related to extrapyramidal disorder was similar across different age groups in the pediatric population (age range 7 months to 17 years old, mean 13 years old).

1.3.3.7. Discussion on clinical safety

The safety profile from the two clinical studies supportive of the intended indication in Bipolar I disorders (10 years and older) appeared to be similar in events to the one observed in the adult population. The short and medium term features of the studies, however did not allow to make any conclusions, particularly for the high rate of EPS symptoms and of weight gain observed in this population.

In the pivotal study 31-03-240, the majority of TEAEs were mild or moderate in severity. Neurologic gastrointestinal AEs and psychiatric AEs not related to lack of efficacy (including aggression, bipolar disorder, libido increased, oppositional defiant disorder and suicidal ideation) were mainly reported. However, somnolence and fatigue were commonly reported (24.5% and 11.8% , respective) and are of concern in the proposed population, younger than the authorised paediatric indication for schizophrenia.

The percentage of subjects who experienced severe TEAEs during the entire study was higher in the aripiprazole arms compared to the placebo arm. The percentage of subjects who discontinued study medication due to TEAEs was greatest in the aripiprazole 30 mg arm, followed by the aripiprazole 10 mg and the placebo arm. For the majority of TEAEs, no dose-relationship could be established, however, EPS symptoms were very significant AEs and dose dependent, with more than quarter of the patients experiencing EPS in the 30 mg aripiprazole arm.

According to previous discussion on efficacy (see 2.3.2.4), the CHMP considered that the MAH proposal to have a maximum daily dose of 30 mg was not acceptable, especially given its safety profile and the intended use in a population, younger than the authorised paediatric indication for schizophrenia.

Weight gain is possibly the most significant AE reported, particularly in bipolar disorders. Although in the acute phase the difference is not statistically significant, there is nonetheless a difference, which appeared clinically relevant, meaning that for most patients weight gain / increased appetite started immediately after initiation of treatment. Increased weight in such short time cannot be attributed to growth, and even small weight increases may represent a significant percentage of weight increase in lighter subjects. At week 30, there was a mean 6.5 Kg increase in aripiprazole treatment arms versus 3.0 Kg increase in placebo.

Potentially clinically significant weight gain (≥ 7% weight gain compared to baseline), was over 30% and reached 44% in studies 31-03-240 and 31-03-241, respectively.

On the basis of further analyses performed at the CHMP request, a clear weight increase over time of >3.5 Kg as compared to placebo by week 30 was observed for completers. Weight gain was higher in the 10-12 years old particularly on the 30 mg aripiprazole arm (even taking in consideration the increase in placebo arm the difference is 4.9 Kg), but the sample size was small and lacked statistical significance. Patients whose weight increased most were non baseline overweight. Although the sample sizes were small, same trend of weight increased were observed in all analyses performed. BMI showed a similar pattern to weight gain, with the placebo arm also increasing slightly in the younger group, and the greatest BMI increased in the treatment arms. One of 98 (1.0%) subjects in the aripiprazole 10 mg arm showed glycolysated haemoglobin increased during the acute phase. None was reported in study 31-03-241. Hyperglycaemia / diabetes usually takes longer to develop than the duration of the studies, therefore no conclusions on these AEs can be made, although this event has been identified as potential concern. In the 30 week period, other metabolic effects were not overly seen, apart from an increase in triglycerides but with high intersubject variability.

In order to address the CHMP concerns over the AE profile observed in the bipolar I disorder population aged 10 years and older, ie high frequency of EPS related symptoms, somnolence and weight gain related events, the MAH presented a comparison of the safety profile for 10-12 years and 13-17 years to support their proposal to revise the indication applied for from 10-17 years to 13-17 years (see Table 21). This analysis provided further evidence that the frequency of EPS, weight gain and somnolence reported in the 10-12 years old group precluded an indication in this younger population. Most AEs occurred with 30 mg aripiprazole than with 10 mg dose.

Comparative data on EPS, sedation, somnolence and weight/BMI changes between age groups of 13-14 years versus 15-17 years did not show any significant differences in AE profiles, suggesting that a restriction to 15-17 years population would not be an appropriate measure to minimise these risks.

Overall, the CHMP concluded that the safety profile was unfavourable for the 10-12 age group and therefore agreed to restrict the indication to the adolescents aged 13 years and older, as proposed by the applicant.). Long term studies are also ongoing that will collect further data to monitor the safety profile of the product in this population.

The CHMP also recommended that educational materials are provided to patients/caregivers to ensure the safe and effective use of Abilify in this new paediatric indication (see 2.3.4).

1.3.4. Risk management plan

The MAH submitted an updated Risk Management Plan (version 7.4) within this variation procedure which included a risk minimisation plan.

Table 26.Summary of the risk management plan (including the changes related to the application presented highlighted)

Safety Issues	Agreed PV Activities	Agreed Risk Minimization Activities (Routine and Additional)
Important Identified Risks:		
EPS, including tardive dyskinesia	Routine PV as listed in the current RMP Additional PV activities: 1. Long-term Maintenance Randomized Placebo Controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Aripiprazole as Maintenance Treatment in Adolescent Patients with Schizophrenia (Protocol No. 31-09-266) will assess AEs, including EPS and tardive dyskinesia 2. Long-term (up to 2 years), Multicenter, Open-Label Study to Evaluate the Safety and Tolerability of Flexible-Dose Oral Aripiprazole as Maintenance Treatment in Adolescent Patients	- Warnings & Precautions, section 4.4 of SmPC: "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 the SmPC: "Nervous system disorders - Common: extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache." "Dystonia: Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups,may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these

Safety Issues	Agreed PV Activities	Agreed Risk Minimization Activities (Routine and Additional)
	with Schizophrenia and Children and Adolescent Patients with Bipolar Disorder (Protocol No. 31-09-267) will assess AEs, including EPS and tardive dyskinesia	symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups." ***Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older:*** **The frequency and type of undesirable effects in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly (≥ 1/10) somnolence (23.0%), extrapyramidal disorder (18.4%), akathisia (16.0%), and fatigue (11.8%); and commonly (≥ 1/100, < 1/10) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia.** **Section 4.4: Special warnings and precautions for use: Other extrapyramidal symptoms: in paediatric clinical trials of aripiprazole akathisia and parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking ABILIFY, dose reduction and close clinical monitoring should be considered.**
	3. Post-authorization safety study to assess the effectiveness of the educational program (e.g., whether the educational material effectively communicates and reinforces the core safety messages conveyed in the SmPC and PIL to carefully consider the indicated age range, dose, and duration of treatment before considering aripiprazole for patients with pediatric bipolar disorder)	**Additional Risk Minimization activities: Physician and Patient/Caregiver Education at the time of product launch for the indication of Bipolar I Disorder in adolescents aged 13 years and older urging vigilance in the ongoing evaluation of extrapyramidal symptoms, weight gain, and AEs related to somnolence/fatigue.**
NMS	Routine PV as listed in the current RMP Additional PV activities: AEs, including NMS, will be monitored in the placebo-controlled efficacy study and the open-label safety	- Warnings & Precautions, section 4.4 of SmPC: "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

Safety Issues	Agreed PV Activities	Agreed Risk Minimization Activities (Routine and Additional)
	study (Protocol Nos. 31-09-266 and 31-09-267).	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." - Undesirable effects, section 4.8 of SmPC - Post-Marketing subsection: Nervous system disorders: speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion.
Potential Risks:		
Seizures	Routine PV as listed in the current RMP	- Warnings & Precautions, section 4.4 of SmPC: "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." - Undesirable effects, section 4.8 of SmPC - Post-Marketing subsection: Nervous system disorders: speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion"
Weight gain	Routine PV as listed in the current RMP **Additional PV activities:** 1. Weight gain, including age- and sex-adjusted z scores, will be monitored in the placebo-controlled efficacy study and the open-label safety study (Protocol Nos. 31-09-266 and 31-09-267) **2. Post-authorization safety study to assess the effectiveness of the educational program (e.g., whether the educational**	Warnings & Precautions, section 4.4 of SmPC: 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 in adults (see section 5.1). **In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in**

Safety Issues	Agreed PV Activities	Agreed Risk Minimization Activities (Routine and Additional)
	material effectively communicates and reinforces the core safety messages conveyed in the SmPC and PIL to carefully consider the indicated age range, dose, and duration of treatment before considering aripiprazole for patients with pediatric bipolar disorder)	adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8). Undesirable Effects, section 4.8 of SmPC: Weight increased is reported as common (≥ 1/100, < 1/10). *Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older:* The frequency and type of undesirable effects in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly (≥ 1/10) somnolence (23.0%), extrapyramidal disorder (18.4%), akathisia (16.0%), and fatigue (11.8%); and commonly (≥ 1/100, < 1/10) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia. Mean changes in body weight in adolescents with Bipolar I Disorder at 12 and 30 weeks for aripiprazole were 2.4 kg and 5.8 kg, and for placebo 0.2 kg and 2.3 kg, respectively. Additional risk minimization activities: physician and patient/caregiver education at the time of product launch for the indication of Bipolar I Disorder in adolescents aged 13 years and older urging vigilance in the ongoing evaluation of extrapyramidal symptoms, weight gain, and AEs related to somnolence/fatigue.
Somnolence and fatigue	Routine PV as listed in the current RMP Additional PV activities: 1. Somnolence and fatigue will be monitored in the placebo-controlled efficacy study and the open-label safety study (Protocol Nos. 31-09-266 and 31-09-267). 2. Post-authorization safety study to assess the effectiveness of the educational program (e.g., whether the educational	Posology and method of administration, section 4.2 of SmPC: The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and at 30 mg is associated with a substantially higher incidence of significant undesirable effects including EPS related events, somnolence, fatigue and weight gain (see section 4.8). Effects on ability to drive and use machines, section 4.7 of SmPC: Some paediatric patients with Bipolar I disorder have an increased

Safety Issues	Agreed PV Activities	Agreed Risk Minimization Activities (Routine and Additional)
	material effectively communicates and reinforces the core safety messages conveyed in the SmPC and PIL to carefully consider the indicated age range, dose, and duration of treatment before considering aripiprazole for patients with pediatric bipolar disorder)	**incidence of somnolence and fatigue (see section 4.8).** **Undesirable effects, section 4.8 of SmPC: In the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia.** **Additional risk minimization activities: physician and patient/caregiver education at the time of product launch for the indication of Bipolar I Disorder in adolescents aged 13 years and older urging vigilance in the ongoing evaluation of extrapyramidal symptoms, weight gain, and AEs related to somnolence/fatigue.**
Hyperglycemia/ diabetes	Routine PV as listed in the current RMP Additional PV activities: Hyperglycemia/diabetes will be monitored in the placebo-controlled efficacy study and the open-label safety study (Protocol Nos. 31-09-266 and 31-09-267).	- Warnings & Precautions, section 4.4 of SmPC: "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." - Undesirable effects, section 4.8 of SmPC - Post-Marketing subsection: Endocrine disorders: hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma.
Suicide	Routine PV as listed in the	- Warnings & Precautions, section 4.4 of SmPC: "The

Safety Issues	Agreed PV Activities	Agreed Risk Minimization Activities (Routine and Additional)
	current RMP Additional PV activities: Suicidality will be monitored in the placebo-controlled efficacy study and the open-label safety study (Protocol Nos. 31-09-266 and 31-09-267).	occurrence of suicidal behaviour 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 suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder." - Undesirable effects, section 4.8 of SmPC - Post-Marketing subsection: Psychiatric disorders: agitation, nervousness; suicide attempt, suicidal ideation, and completed suicide (see section 4.4)
Orthostatic hypotension (aripiprazole solution for injection)	Routine PV as listed in the current RMP Additional PV activities: Orthostatic hypotension will be monitored in the placebo-controlled efficacy study and the open-label safety study (Protocol Nos. 31-09-266 and 31-09-267).	Warnings & Precautions, section 4.4 of SmPC 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 Additional PV activities: Two trials, including Protocol nos. 31-09-266 and 31-09-267, will assess the presence of baseline, treatment, and end of study fasting lipids, including cholesterol and triglycerides.	Undesirable effects, section 4.8 of SmPC: Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no medically important differences. Lipid parameters: In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and LDL. -Total cholesterol: incidence of changes in levels from normal (<5.18 mmol/l) to high (≥ 6.22 mmol/l) was 2.5% for aripiprazole and 2.8% for placebo and mean change from baseline was -0.15 mmol/l (95% CI: -0.182, -0.115) for aripiprazole and -0.11 mmol/l (95% CI: -0.148, -0.066) for placebo. - Fasting triglycerides: incidence of changes in levels from normal (< 1.69 mmol/l) to high (≥ 2.26 mmol/l) was 7.4% for aripiprazole and 7.0% for

Safety Issues	Agreed PV Activities	Agreed Risk Minimization Activities (Routine and Additional)
		placebo and mean change from - baseline was -0.11 mmol/l (95% CI: -0.182, -0.046) for aripiprazole and -0.07 mmol/l (95% CI: -0.148, 0.007) for placebo. -HDL: incidence of changes in levels from normal (≥ 1.04 mmol/l) to low (< 1.04 mmol/l) was 11.4% for aripiprazole and 12.5% for placebo and mean change from baseline was -0.03 mmol/l (95% CI: -0.046, -0.017) for aripiprazole and -0.04 mmol/l (95% CI: -0.056, -0.022) for placebo. -Fasting LDL: incidence of changes in levels from normal (< 2.59 mmol/l) to high (≥ 4.14 mmol/l) was 0.6% for aripiprazole and 0.7% for placebo and mean change from baseline was -0.09 mmol/l (95% CI: -0.139, -0.047) for aripiprazole and -0.06 mmol/l (95% CI: -0.116, -0.012) for placebo.
Cardiovascular-related disorders	Routine PV as listed in the current RMP	- Warnings & Precautions, section 4.4 of SmPC: "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." - Undesirable effects, section 4.8 of SmPC - Post-Marketing subsection: "Cardiac disorders: QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes, bradycardia. Vascular disorders: syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)"
Conduction abnormalities	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SmPC: "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." Undesirable effects, section 4.8 of SmPC - Post-Marketing subsection: "Cardiac disorders: QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes, bradycardia."

Safety Issues	Agreed PV Activities	Agreed Risk Minimization Activities (Routine and Additional)
Growth	Routine PV as listed in the current RMP Additional PV activities: Height will be monitored in the placebo-controlled efficacy study and the open-label safety study (Protocol Nos. 31-09-266 and 31-09-267).	None
Low prolactin in paediatric patients	Routine PV as listed in the current RMP Additional PV activities: 1. Long-term (up to 2 years) efficacy and safety maintence trial of adolescent patients with schizophrenia (Protocol No. 31-09-266). 2. Long-term (up to 2 years), open-label safety study of maintenance treatment in adolescent patients with schizophrenia and children and adolescent patients with bipolar disorder (Protocol No. 31-09-267).	Undesirable effects, section 4.8 of SmPC - Paediatric Population subsection: In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (< 3 ng/ml) and males (< 2 ng/ml) was 29.5% and 48.3%, respectively. Section 4.8 of SmPC for paediatric bipolar patients: In the paediatric bipolar population (10-17 years) with exposure up to 30 weeks, incidence of low serum prolactin levels in females (< 3 ng/ml) and males (< 2 ng/ml) was 28.0% and 53.3%, respectively.
Dysphagia (primarily applies to schizophrenia population)	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SmPC: "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	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SmPC: "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."
ADHD comorbidity	**Routine PV as listed in the current RMP**	**Patients with ADHD comorbidity: despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of ABILIFY and stimulants; therefore, extreme caution should be taken when these drugs are co-administered.**
Drug interactions	Routine PV as listed in the	Drug interaction information in section 4.5 of the

Safety Issues	Agreed PV Activities	Agreed Risk Minimization Activities (Routine and Additional)
	current RMP	SmPC: P2D6, 3A4 :ihypertensives ohol or other CNS medications ıgs prolonging QT or causing electrolyte)alance antagonist
Increased mortality and CVA in elderly patients with dementia	Routine PV as listed in the current RMP	Warnings & Precautions, section 4.4 of SmPC: "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 AEs reports	None
Serious hypersensitivity reactions to excipients (with Solution for Injection only)	Continue monitoring post-marketing AEs reports	None

Safety Issues	Agreed PV Activities	Agreed Risk Minimization Activities (Routine and Additional)
Pathological gambling	Continue monitoring post-marketing AEs reports	Warnings and precautions, section 4.4 of SmPC: Pathological gambling: rare reports of pathological gambling have been reported post-marketing among patients prescribed ABILIFY. Patients with a prior history of pathological gambling may be at increased risk and should be monitored carefully (see section 4.8). Undesirable effects, section 4.8 of SmPC: Pathological gambling is added as a post marketing adverse reaction.
Missing Information		
Pregnancy and lactation	Routine PV as listed in the current RMP	Pregnancy and lactation, section 4.6 of the SmPC: "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. Neonates exposed to antipsychotics (including aripiprazole) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. 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 breast feed if they are taking aripiprazole."
Pediatrics	Routine PV and additional PV activities as written in the current RMP	ORAL FORMULATIONS - Therapeutic indications for paediatric patients in section 4.1 of the SmPC: "ABILIFY is indicated for the treatment of schizophrenia in adolescents 15 years and older."

Safety Issues	Agreed PV Activities	Agreed Risk Minimization Activities (Routine and Additional)
		- Posology and method of administration information for paediatric patients in section 4.2 of the SmPC: *"Schizophrenia in adolescents 15 years and older:* ABILIFY is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1). - *Irritability associated with autistic disorder:* the safety and efficacy of ABILIFY in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made. ***Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older:*** **Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, ABILIFY is not recommended for use in patients below 13 years of age (see sections 4.8 and 5.1).** **Additional risk minimization activities: physician and patient/caregiver education at the time of product launch for the indication of Bipolar I Disorder in adolescents aged 13 years and older urging vigilance in the ongoing evaluation of extrapyramidal symptoms, weight gain, and AEs related to somnolence/fatigue.**

The below pharmacovigilance activity in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Aripiprazole Risk Minimization Tool Evaluation Survey to evaluate the effectiveness of the aripiprazole risk minimization (RM) educational material in terms of awareness , utilization, knowledge, and comprehension of the educational material and appropriate behavior by healthcare professionals (HCPs) and patients.	Full protocol by Q2 2013

This pharmacovigilance activity is in addition to those already requested (studies 31-09-266 and 31-09-267).

The following additional risk minimisation activities were required:

In each Member State where the new indication of ABILIFY for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older is launched the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority. The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where the new indication of ABILIFY for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older is launched all healthcare professionals who are expected to prescribe ABILIFY are provided with an information pack containing the following items:

- Summary of Product Characteristics (SmPC) and Package Leaflet
- Educational material for the healthcare professionals
- Educational material for the patients and their caregivers

Key elements of the Healthcare Professional FAQ Brochure (Q&A format) intended for Healthcare Providers treating adolescent patients with bipolar mania:

- Brief introduction to aripiprazole indication and the purpose of the tool.
- Instructions reinforcing that the indicated age range is 13 – 17 years and that aripiprazole is *not* recommended for use in patients below 13 years of age due to safety concerns
- Instructions that the recommended dose is 10 mg/day and that enhanced efficacy at higher doses has not been demonstrated
- Information regarding the safety and tolerability profile of aripiprazole, in particular potential consequences regarding adverse effects at doses higher than 10 mg/day, in particular with respect to:
  - Weight gain, including a recommendation to monitor patients
  - Extrapyramidal symptoms
  - Somnolence
  - Fatigue
- Reminder to educate patients/caregivers and distribute the Patient/Caregiver Information Brochure

Key elements of the patients/caregiver Information Brochure:

- Brief introduction to aripiprazole indication and the purpose of the tool.
- Information that the indicated age range is 13 – 17 years and that aripiprazole is *not* recommended for use in patients below 13 years of age
- Information that aripiprazole can cause adverse effects at doses higher than 10 mg/day, in particular with respect to:
  - Weight gain, including a recommendation to monitor patients
  - Extrapyramidal symptoms
  - Somnolence
  - Fatigue
- Request to inform the physician of all medical conditions before treatment.
- The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional

2. BENEFIT RISK ASSESSMENT

2.1.1. Benefits

2.1.1.1. Beneficial effects

Results from study 31-03-240, a large randomised controlled trial conducted in children and adolescents aged 10 years and older, showed that aripiprazole is effective in the treatment of moderate to severe manic episodes, as demonstrated by statistically significant improvement compared with placebo in the primary efficacy endpoint, the mean change from baseline to week 4 in the total YMRS score. The study was a double blind placebo controlled consisting of an acute 4 week phase and a 26 week maintenance phase. The duration of the study was therefore longer than the recommended 12 week maintenance trial as referred in the "Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Bipolar Disorder", (CPMP/EWP/567/98). Significant improvements were also documented for the secondary efficacy endpoints: CGAS, CGI-BP Severity Score for mania and for overall bipolar illness, GBI Total Score for mania and for the ADHD rating scale.

In the acute phase, treatment with aripiprazole resulted in statistically significant improvements (LOCF) compared with placebo in the primary efficacy endpoint YMRS Total Score at week 4 in both 10 mg (-5.99, CI:-8.49;-3.50, p<0.0001) and 30 mg (-8.26, CI:-10.7;-5.77, p<0.0001).

This efficacy was maintained through week 30 showing a statistically significant sustained improvement over placebo in both 10 mg (-5.89, CI:-8.70;-3.08, p<0.0001) and 30 mg (-6.73, CI:-9.53;-3.94, p<0.0001). Mean changes in YMRS Total Scores at week 30 using LOCF data were −14.1 in the aripiprazole 10 mg arm, −14.9 in the aripiprazole 30 mg arm, and −8.2 in the placebo arm.

Significant improvements were also documented for the secondary efficacy endpoints: CGAS, CGI-BP Severity Score for mania and for overall bipolar illness, GBI Total Score for mania and for the ADHD rating scale

Both the aripiprazole 10 mg and 30 mg arms had significantly higher percentages of responders compared to the placebo arm at every treatment week during both at week 4 and at week 30 using the LOCF data set, thus showing maintenance of the effect of treatment. At week 4, percentages of responders were 44.79 % and 63.64% for 10 and 30 mg groups as compared to 26.09% for the placebo group. At week 30, percentages of responders were around 50% and 55.56% for 10 and 30 mg groups as compared to 26.6% for the placebo group.

2.1.1.2. Uncertainty in the knowledge about the beneficial effects

In a post-hoc analysis, the population without comorbid disorders did not differ significantly in mean change of YMRS in both 10 mg aripiprazole and placebo by week 4 thus questioning as to whether aripiprazole may act mainly in symptoms common to ADHD / ODD and not specifically on Bipolar Disorder type I. Additional subgroup analyses were performed indicating that the presence of any comorbidity did not seem to influence the YMRS changes at weeks 4 and 12. However, the persistence of effect was less evident in patients with or without ADHD at both weeks 4 and 12 for the 30 mg dose.

When compared to the placebo at week 12, the OC analysis failed to show statistical significant over the placebo for both doses on all analysed efficacy endpoints for both age groups. Considering the high rates of discontinuation, the CHMP considered that the OC analysis did not provide any relevant

findings apart that a significant percentage of patients did improve spontaneously by week 12, suggesting that the treatment should not be prolong longer than 12 weeks.

For efficacy endpoints evaluating the effect of treatment on depressive symptoms (CGI-BP Severity Score for depression, GBI Total Score for depression and CDRS) no statistically significant superiority of aripiprazole over placebo treatment was observed.

2.1.2. Risks

2.1.2.1. Unfavourable effects

The safety profile from the two clinical studies supportive of the intended initial indication in Bipolar I disorders (10 years and older) appeared to be similar in events to the one observed in the adult population. High rate of EPS symptoms and weight gain and somnolence are of particular concern in the proposed population.

Potentially clinically significant weight gain reached 30% in study 31-03-240 and 44% in study 31-03-241, reflecting a very high risk of weight gain associated with a morbid status, particularly in a bipolar population.

EPS symptoms, particularly parkinsonism was very frequent and dose dependent to aripiprazole. If moderate or severe, these symptoms will be a stigma to subjects, and slowness of movements and thought will have impact in patient's activities of daily living and quality of life.

Somnolence/fatigue was also very frequent and can have a deleterious effect on school attendance and school achievements.

2.1.2.2. Uncertainty in the knowledge about the unfavourable effects

No paediatric data on the long term effect of aripiprazole (e.g on weight gain and EPS) are currently available. Long term safety studies are ongoing to monitor the safety profile in this population.

2.1.2.3. Balance

2.1.2.4. Importance of favourable and unfavourable effects

Efficacy was demonstrated over placebo in Bipolar I disorder patients aged 10-17 years old at week 4 as shown by statistically significant improvement on the total YRMS score. This efficacy was maintained through week 30 showing a statistically significant sustained improvement over placebo in both 10 mg and 30 mg. However, when compared to the placebo at week 12, the OC analysis failed to show statistical significant over the placebo for both doses on all analysed efficacy endpoints for both age groups of 10-12 and 13-17 years. Given the high number of discontinuation, this finding suggested that the treatment should not be prolong longer than 12 weeks.

Whilst the CHMP noted the standardised measures put in place for diagnosis based on DSM-IV criteria, a post-hoc analysis showed that the population without comorbid disorders did not differ significantly in mean change of YMRS in both 10 mg aripiprazole and placebo by week 4 thus questioning as to whether aripiprazole might act mainly in symptoms common to ADHD / ODD and not specifically on Bipolar Disorder type I. However, additional subgroup analyses were performed indicating that the presence of any comorbidity did not seem to influence the YMRS changes at weeks 4 and 12, this was being less evident with patients with or without ADHD at both weeks 4 and 12 for the 30 mg dose. In addition, further analysis were presented showing that ADHD status did not change the 10 mg

treatment effect significantly, particularly at week 12, where the use of ADHD medication was already permitted and favoured aripiprazole effect independently the presence of ADHD or ADHD medication.

The available data to date raised safety concerns regarding mostly weight gain, EPS symptoms, especially in the young Bipolar I disorder population aged 10-12 years. Most AEs occurred with 30 mg aripiprazole than with 10 mg dose. Since enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, the use of the 30 mg dose was not recommended by the CHMP, and an increase over 10 mg should only be performed under strict surveillance.

2.1.2.5. Benefit-risk balance

Considering the efficacy and safety data across paediatric age groups from 10-17 years, the CHMP noted that the safety profile was not favourable for the younger population (10-12 years) and therefore concluded that the benefit –risk balance was positive in the paediatric Bipolar I disorder population aged 13 years and older. In order to minimise the risks of dose-related AEs occurrence, the use of the 30 mg dose is not recommended by the CHMP, and an increase over 10 mg should only be performed under strict surveillance. In addition, educational material will be provided to patients and caregivers to ensure the safe and effective use of Abilify in this new paediatric indication.

2.2. Conclusions

The overall benefit-risk balance of Abilify is positive for the following indication: "ABILIFY is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older (see section 5.1)".

3. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends , by a majority of 24 out of 28 votes, the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

Divergent positions to the majority recommendation are appended to this report.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP shall be submitted annually.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

- **Additional risk minimisation measures**

In each Member State where the new indication of ABILIFY for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older is launched the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority. The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where the new indication of ABILIFY for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older is launched all healthcare professionals who are expected to prescribe ABILIFY are provided with an information pack containing the following items:

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  - Weight gain, including a recommendation to monitor patients
  - Extrapyramidal symptoms
  - Somnolence
  - Fatigue

- Reminder to educate patients/caregivers and distribute the Patient/Caregiver Information Brochure

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  - Extrapyramidal symptoms
  - Somnolence
  - Fatigue
- Request to inform the physician of all medical conditions before treatment.
- The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional

Appendix

Divergent Positions

DIVERGENT POSITIONS

The undersigned members of CHMP did not agree with the CHMP's positive opinion recommending the variation to the marketing authorisation to add the following indication: "ABILIFY is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older (see section 5.1)." The reasons for divergent opinion were the following:

- The efficacy of aripiprazole in the treatment of manic or mixed episodes of type 1 bipolar mood disorder has not been shown; the treatment effects largely disappeared after exclusion of psychiatric comorbid disorders suggesting the effect is mediated by a possibly aspecific effect on symptoms due to comorbidity hence at least questioning the effect on symptoms of mania in adolescents;

- The safety profile (occurrence of EPS symptoms, weight gain and somnolence) is unfavourable in younger patients aged 13 years and older with manic episode, especially taking the above into account.

London, 13 December 2012

Concepcion Prieto Yerro	
Barbara van Zwieten-Boot	
Hubert Leufkens	
Sol Ruiz	