24 July 2014
EMA/557557/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abilify

International non-proprietary name: ARIPIPRAZOLE

Procedure No. EMEA/H/C/000471/II/0101

Note

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

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Background information on the procedure

Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Otsuka Pharmaceutical Europe Ltd submitted to the European Medicines Agency on 4 March 2014 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Abilify	aripiprazole	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The MAH proposed the update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SPC) to include information related to studies 31-12-293 and 031-KOA-0703 conducted in patients (6-18 years) with Tourette's disorder (TD).

The requested variation proposed amendments to the Summary of Product Characteristics.

Rapporteur: Bruno Sepodes

Steps taken for the assessment

Submission date:	4 March 2014
Start of procedure:	23 March 2014
Rapporteur's preliminary assessment report circulated on:	24 April 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	22 May 2014
MAH's responses submitted to the CHMP on:	24 June 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	7 July 2014
CHMP opinion:	24 July 2014

2. Scientific discussion

2.1 Introduction

Aripiprazole, a dihydrocarbostyril (quinolinone) derivative, is an antipsychotic agent. Aripiprazole (Abilify) was authorised in the European Union (EU) on 4 June 2004. Aripiprazole tablets, orodispersible tablets and oral solution are currently approved in the EU for the treatment of schizophrenia in adults with recommended starting dose of 10 mg or 15 mg/day and target dose of 15 mg/day administered on a once-a-day schedule without regard to meals. These formulations are also indicated for the treatment of moderate to severe manic episodes in Bipolar I disorder and for the prevention of a new manic episode in adult patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

Abilify tablets, orodispersible tablets and oral solution are also approved in the EU for the treatment of schizophrenia in adolescents 15 years and older and in the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older. The recommended dose in these patient groups 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. When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg for adolescents 15 years and older with schizophrenia. In adolescents aged 13 years and older with Bipolar I disorder, 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. Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring.

Aripiprazole intramuscular (7.5mg/ml, solution for injection) is specifically indicated for the treatment of the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate.

The present application does not concern aripiprazole intramuscular (7.5 mg/ml, solution for injection).

This variation refers to update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SmPC) to include information related to studies 31-12-293 and 031-KOA-0703 conducted in patients (6-18 years) with Tourette's disorder (TD).

2.2 Clinical efficacy aspects

Tourette’s Disorder (TD) is a neuropsychiatric disorder that is characterized by childhood onset of motor and phonic tics. A dopaminergic hyperfunction in certain brain areas in Tourette’s Disorder would explain why postsynaptic dopamine antagonists such as antipsychotics as well as dopamine agonists with a presynaptic component may be effective in suppressing tics associated with TD.

From epidemiological studies it is likely that the prevalence of TD in the general population ranges from 4.3 to 10 per 10,000 but may be as high as 100 per 10,000 in children between 8 and 12 years of age.

The main characteristics of TD appear to be independent of culture and, in general, symptoms are similar worldwide. TD is found in all countries, all racial groups and is three to four times more common in males. Disability caused by TD however, is strongly related to the type of tics and social environment, and the extent to which tics may interfere with social role of the patient.

Although the precise etiology of TD remains unknown, disturbances in dopaminergic and/or serotonergic pathways have been implicated because of the close association between TD and other disorders that involve imbalances in dopamine and/or serotonin (eg, obsessive-compulsive disorder [OCD] and attention deficit disorder/attention-deficit/ hyperactivity disorder [ADD/ADHD]). Regarding such disorders, ADHD and OCD are the most prevalent comorbidities and occur in 84% of individuals with TD.

The rationale for studying aripiprazole in TD is the fact that it exhibits partial agonism at dopamine D2 and serotonin 5-hydroxytryptamine (5-HT)1A receptors and antagonism at serotonin 5-HT2 receptors. The currently available tablet formulation for daily administration has been investigated for the treatment of children and adolescents with tic disorders, including those with TD, in a few uncontrolled trials. Most used agents do not have an approved indication in TD, including antipsychotics. Pimozide, the most extensively used does not have an indication in TD in several countries. Haloperidol is also used, and more recently risperidone and ziprasidone have also been used. The use is usually based upon small short term non controlled clinical trials or case descriptions. Antipsychotic safety profile often preclude its widespread and long term use.

Within this application, the MAH submitted 2 completed paediatric studies, 31-12-293 and 031-KOA-0703 conducted in patients (6-18 years) with Tourette's disorder (TD) in accordance to article 46 of Paediatric Regulation 1901/2006, as amended:

- Trial 31-12-2931: A multicentre, randomised, double blind, placebo controlled study enrolling patients in Hungary, Italy, Canada, and US to evaluate the safety and efficacy of fixed dose once daily oral aripiprazole in children and adolescents with Tourette’s disorder;
- Trial 031-KOA-07032: A randomised, double-blind, dose-adjustment, placebo-controlled study conducted in Korea to evaluate the efficacy and safety of aripiprazole in children and adolescents with chronic Tic disorders or Tourette’s disorder.

On the basis of these data, the MAH proposed to update the SmPC information for Abilify.

2.2.1 Methods – analysis of data submitted

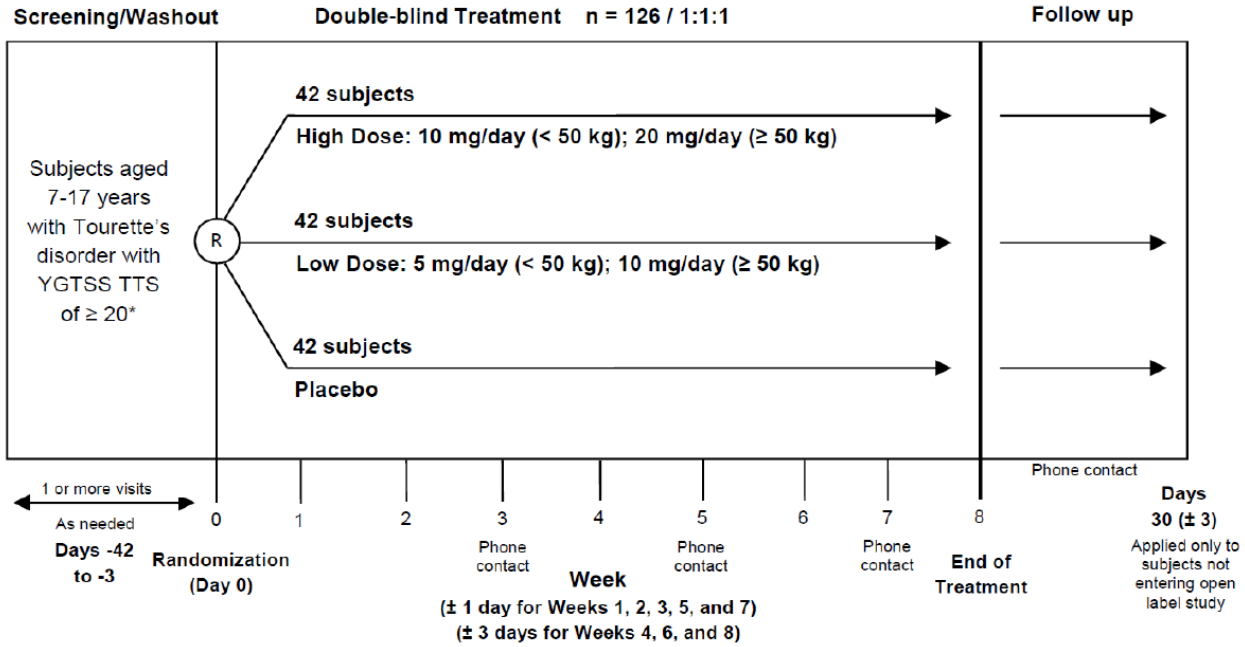
2.2.1.1 Study Design

Although of similar overall design, there were differences in the dosing schemes and titration schedules for the 2 trials. In both trials, all subjects were randomly assigned to active treatment or placebo. Trial 31-12-293 evaluated fixed dosing in an 8-week trial conducted globally and Trial 031-KOA-0703 evaluated flexible dosing in a 10-week trial conducted in Korea. All subjects assigned to active treatment in both trials began with a dose of 2 mg/day.

Trial 31-12-293

Trial 31-12-293 was a phase 3, multicentre, randomised, double blind, placebo controlled, outpatient trial designed to assess the safety and efficacy of fixed dose oral aripiprazole once daily tablets in children and adolescents with Tourette’s disorder.

Figure: Trial design schematic



Subjects were male or female children or adolescents between 7 and 17 years of age (inclusive) who met the current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM IV TR) diagnostic criteria for Tourette's disorder (as confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K SADS PL), including the Diagnostic Supplement 5 [Substance Abuse and Other Diseases, i.e., Tic Disorders]), had a total Tic score ≥ 20 on the Yale Global Tic Severity Scale (YGTSS) at screening and baseline (randomisation), and who, along with his/her caregiver, and the investigator all agreed that the presenting tic symptoms caused impairment in the subject's normal routines (e.g., academic achievement, occupational functioning, social activities, and/or relationships). Subjects did not have neurologic conditions that may have abnormal movements (e.g., Transient Tic disorder, Huntington's disease) and had no history of psychotic disorder or bipolar disorder. Subjects were in good physical health as determined by medical history, clinical laboratory tests, electrocardiogram (ECG), and physical examinations. The eligibility criteria were developed to represent the patient population that would most likely be treated with aripiprazole tablets. The subjects enrolled allowed for the appropriate evaluation of efficacy in the intended population.

The trial consisted of 2 distinct phases: Pre-treatment phase consisting of a screening and washout (when applicable) period, followed by 8 week treatment phase starting with the baseline visit (Day 0). There was also a follow up period (30 ± 3 days) for subjects who discontinued from the trial or who did not roll over into an open label follow-on trial (Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) protocol 31 12 294).

Subjects were randomised 1:1:1 to low or high dose aripiprazole or placebo. For subjects who weighed < 50 kg at baseline, low and high doses of aripiprazole were 5 and 10 mg/day, respectively. For subjects who weighed ≥ 50 kg at baseline, low and high doses of aripiprazole were 10 and 20 mg/day, respectively. All subjects randomised to the aripiprazole groups began treatment at a 2 mg/day dose, with the dose titrated to 5 mg/day after 2 days. The dose was titrated to achieve the randomised dose according to a pre-specified titration scheme. All subjects reached their randomised dose by Week 3 and remained on that randomised dose. If a subject did not tolerate the randomised dose during the titration period (before first dose at Week 3), he/she was discontinued from the trial. If a subject did not tolerate the randomised dose, the dose may have been decreased one time after Week 3, to the next lower dose level or to 2 mg/day for the 5 mg/day group. Subjects who did not tolerate the reduced dose were discontinued from the trial.

Trial 031-KOA-0703

Trial 031-KOA-0703 was a randomised, double-blind, dose-adjustment, placebo-controlled study conducted in South Korea to evaluate the efficacy and safety of aripiprazole in children and adolescents with chronic Tic disorders or Tourette's disorder. Subjects were male or female children and adolescents aged 6 to 18 years (inclusive) with a current diagnosis of chronic Tic disorders (vocal Tic and motor Tic) or Tourette's disorder according to DSM-IV (using Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version-Korean version (K-SADS-PL-K)) requiring drug therapy. Subjects had equal to or greater than 22 in total Tic scores on the Korean version of Yale Global Tic Severity Scale (K-YGTSS) at baseline visit. Subjects were required to be in good physical health as determined by medical history, clinical laboratory tests, ECG, and physical examinations. The eligibility criteria were developed to represent the patient population that would most likely be treated with aripiprazole tablets and as such the subjects enrolled allowed for the appropriate evaluation of efficacy in the intended population.

Subjects were randomised to either aripiprazole or placebo in a 1:1 ratio and received double-blind study drug for 10 weeks from the randomisation day (Day 1). All subjects visited hospital every 2 weeks, and investigators adjusted the study drug dose according to the improvement of Tic symptoms and incidence of adverse events. The dose increase schedule was from 2 mg/day to 5 mg/day, 10 mg/day, 15 mg/day, and 20 mg/day, and the decision to increase dose was made at each 2 week visit. The maximum target dose was 20 mg/day, but it was not mandatory to reach the maximum dose.

The investigator made the final decision on the dose adjustment based on the improvement of Tic symptoms (score of the Tourette's syndrome-Clinical Global Impression-Improvement (TS-CGI-I) scale) and adverse events based on the following criteria: a) Criteria for maintaining dose: a score of 1 or 2 in the TS-CGI-I scale and tolerable adverse event; b) Criteria for increasing dose: a score of ≥ 3 in the TS-CGI-I scale and tolerable adverse event; c)Criteria for reducing dose: in case of an intolerable adverse event the dose was decreased to the previous dose or study drug was discontinued based at the investigator's discretion. If the dose was decreased from the previous dose, the reduced dose was maintained until the final visit.

An independent data safety monitoring board (DSMB) reviewed and evaluated cumulative safety data collected at regular intervals to ensure the safety of subjects enrolled in the trial.

2.2.1.2 Statistical Methods

Trial 31-12-293

For Trial 31-12-293, the ITT Sample was the primary dataset for all efficacy analyses, and was composed of all subjects randomly assigned to investigational medicinal product (IMP). The statistical analyses of the primary and key secondary endpoints were performed by using a mixed model repeated measures (MMRM) linear model under the assumption that missing data were missing at random (MAR). The MMRM model included terms of treatment (aripiprazole low-dose, aripiprazole high-dose, or placebo), region, body weight group, visit week, and treatment-by-week interactions as fixed categorical effects, and fixed covariate of either baseline YGTSS TTS (for the primary endpoint) or the Clinical Global Impression severity (CGI-S) scale score, with a single unstructured covariance matrix assumed for all treatment groups. Subjects without a post-baseline measurement of YGTSS TTS were not included in the MMRM analysis, but their data were analysed using imputed post-baseline data in the sensitivity analyses assuming a missing not at random (MNAR) scenario (described subsequently in this section). The Hochberg procedure was used to adjust for multiplicity in testing 2 comparisons (low-dose aripiprazole versus placebo and high-dose aripiprazole versus placebo) of the primary endpoint (YGTSS TTS) and key secondary endpoint (CGI-I at endpoint), and form 2 families of null hypotheses in the stated order. The rules following the Hochberg procedure

were as follows: if the maximum of the 2 p-values was < 0.05, then both hypotheses were rejected with claim for statistical significance; otherwise, if the smaller of the 2 p-values was < 0.025, then the hypothesis with the smaller p-value was rejected with claim for statistical significance. Both null hypotheses for the primary endpoint must have been rejected at the 0.05 significance level in order to test the 2 null hypotheses for the key secondary endpoint. Sensitivity analyses of the primary and key secondary endpoints were performed to assess the impact of missing data being MNAR and to understand the impact of stepdown dosing.

Missing data in this trial could potentially have arisen from the mechanism of MNAR. In order to understand the impact on the trial findings of different treatments for missing data under the MNAR assumption, if at least 1 aripiprazole dose group demonstrated statistically significant efficacy, sensitivity analyses of the primary endpoint were carried out by multiple imputations for the ITT Sample.

Trial 031-KOA-0703

For Trial 031-KOA-0703, the ITT Sample was the primary dataset for all efficacy analyses, and was composed of all randomized subjects. Assumption of normality was checked before carrying out statistical testing on continuous variables. If the normality assumption was met, parametric methods (e.g., paired t-test, 2-sample t-test, or analysis of variance were used). If the normality assumption was not met, nonparametric methods (e.g., Kruskal Wallis test, Wilcoxon signed rank test, or Wilcoxon rank sum test) were used. All tests were presented at the 2-tailed, 0.05 level of significance. Missing data were imputed via last-observation carried- forward (LOCF) analysis, and included results for 2 subjects in the placebo group for whom the only post-baseline visit was the ET visit.

2.2.2 Results

2.2.2.1 Patient Population

Trial 31-12-293

A total of 133 subjects were randomised in the trial to either low dose aripiprazole (44 subjects of whom 28 and 16 received aripiprazole 5 and 10 mg, respectively), high dose aripiprazole (45 subjects of whom 30 and 15 received aripiprazole 10 and 20 mg, respectively) or placebo (44 subjects). All randomised subjects received study drug. A total of 119 subjects completed the trial (i.e., completed the Week 8 Visit). The mean age of randomised subjects was 11.1, 11.8, and 11.6 years in the low and high dose aripiprazole and placebo groups, respectively. Overall, the baseline demographic characteristics were similar between the low and high dose aripiprazole and placebo groups with the exception of a higher percentage of Black or African American subjects in the aripiprazole low dose group, and a lower mean body weight at baseline in the low dose aripiprazole group compared with the other groups. The intention to treat (ITT) Sample included a higher percentage of males than females in each of the low and high dose aripiprazole and placebo groups: 81.8%, 77.8%, and 75.0%, respectively. The mean weight and body mass index (BMI) of randomised subjects were 44.2 kg and 19.5 kg/m2, 47.4 kg and 20.3 kg/m2, 47.8 kg and 20.1 kg/m2, respectively, in the low and high dose aripiprazole and placebo groups. Baseline characteristics were also similar between the low and high dose aripiprazole and placebo groups with regards to disease status. The baseline mean total YGTSS of randomised subjects was 61.2, 62.5, and 62.8 in the low and high dose aripiprazole and placebo groups, respectively. The baseline mean Clinical Global Impressions Scale Tourette's Syndrome (CGI TS) Severity Score was 4.3, 4.1, and 4.2 in the low and high dose aripiprazole and placebo groups, respectively.

Trial 031-KOA-0703

A total of 61 subjects were randomised to either placebo (29 subjects) or aripiprazole (32 subjects). All randomised subjects, except for one in the aripiprazole arm who withdrew due to protocol deviation, were treated with the study drug. Demographics were similar across treatment groups. The mean age was 10.95 years (SD ± 2.72; range, 6 to 18 years). All 61 subjects (100.00%) had current psychiatric histories of Tourette's disorder. There were no statistically significant differences between the aripiprazole and placebo groups with regards to other past psychiatric histories or other current psychiatric histories. 54 subjects (25 placebo, 29 aripiprazole) completed the trial and the disposition of study completion status did not differ between the two groups (p=0.6988).

2.2.2.2 Efficacy results

Trial 31-12-293

Primary endpoint

The primary endpoint was the change from baseline to endpoint (Week 8) in the YGTSS TTS. The treatment difference between the low-dose aripiprazole and placebo groups (-6.26) was statistically significant (p = 0.0020) for the primary efficacy variable (change from baseline to Week 8 in YGTSS TTS); the treatment difference between the high-dose aripiprazole and placebo groups (-9.85) was also statistically significant (p < 0.0001), based on a mixed effect repeated measure model. Sensitivity analyses of the primary endpoint corroborated these results.

The onset of a treatment difference between the aripiprazole and placebo groups occurred as early as Week 1 in YGTSS TTS (see below). Separation in the treatment difference between the high-dose aripiprazole and placebo groups increased from Weeks 2 through 8, and between the low-dose aripiprazole and placebo groups from Weeks 4 through 8. The high-dose aripiprazole group demonstrated a numerically greater treatment effect than the low-dose aripiprazole group at each time point in the trial. The treatment difference between the aripiprazole (low and high doses) and placebo groups was statistically significant at all-time points except at Week 2 in the low-dose aripiprazole group.

The LS mean changes from baseline in the YGTSS TTS score by week are shown below:

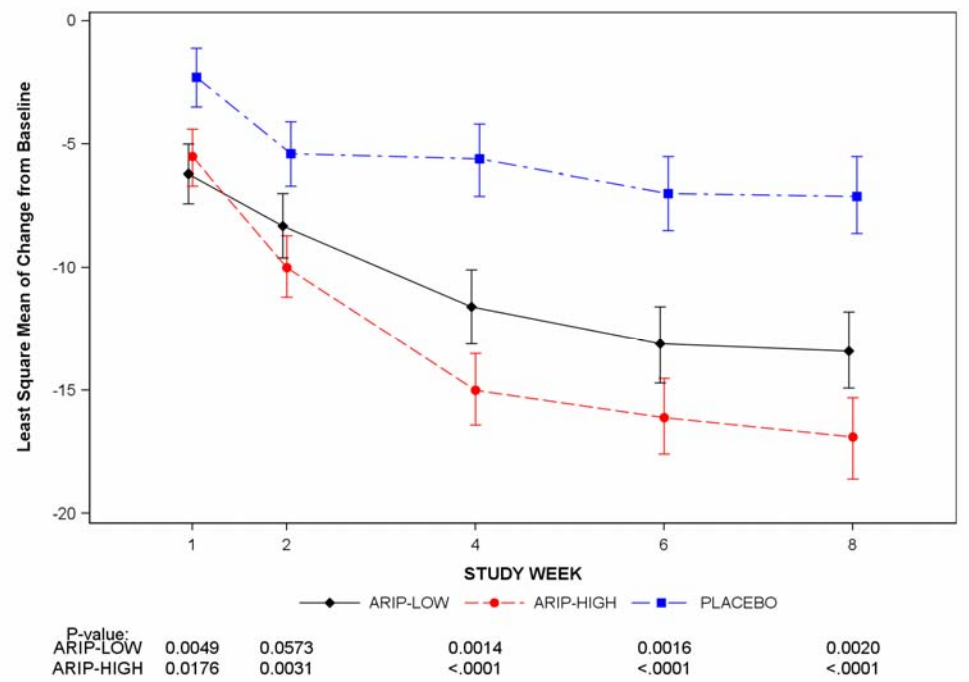


Figure:Least Square Means of Change from Baseline in YGTSS TSS Score By Week

ARIP = aripiprazole.

Error bars are least square means ± 1 standard error.

Table: Analysis of Change from Baseline to Week 8 in YGTSS TTS for Trial 31-12-293, MMRM (ITT Sample)

Treatment Group	N[a]	Baseline Mean	LS Mean[b]	LS Mean SE[b]	Estimated Treatment Effect[b]	95% CI[b] Lower Limit	95% CI[b] Upper Limit	P-value[b]
Aripiprazole-low	42	29.3	−13.35	1.59	−6.26	−10.18	−2.34	0.0020
Aripiprazole-high	35	31.5	−16.94	1.61	−9.85	−13.84	−5.86	< 0.0001
Placebo	42	30.3	−7.09	1.55				

CI = confidence interval; LS = least squares; SE = standard error.

Note: TTS ranges from 0 to 50 with higher score for more severe symptom (greater reduction from baseline for greater improvement).

[a]Number of subjects with baseline and a measurement of YGTSS TTS at Week 8.

[b]Derived from a repeated measures linear model with treatment, week, treatment-by-week interaction, region and weight group as fixed categorical effects, the baseline value as a fixed covariate, and week as the time variable for repeated measures.

Source: CSR 31-12-293 Table 11.4.1.1-1.

The primary efficacy endpoint was analysed for the following subgroups: a) Age of 7 to 12 years versus 13 to 17 years at screening; b) Region of North America (US and Canada) versus the Rest of the World; c) Race of white versus Other; d) Baseline YGTSS TTS of < 30 versus ≥ 30.

The treatment effect among these subgroups was similar to the trial population, except in the "Other" race and the 13-to-17 year-old subgroups for the low-dose aripiprazole versus placebo groups and except in the "Other" race and the "Rest of the World" subgroups for the high-dose aripiprazole versus placebo groups. However, the small sample sizes in these subgroups do not allow reliable inferences to be made.

Secondary endpoints

The key secondary endpoint was the mean CGI-TS Change Score at endpoint (change score obtained from CGI-TS improvement scale assessment). The treatment difference between the low-dose aripiprazole and placebo groups (-1.03) was statistically significant (p = 0.0001) for the key secondary efficacy variable; the treatment difference between the high-dose aripiprazole and placebo groups (-1.02) was also statistically significant (p = 0.0002), based on a mixed effect repeated measure model. Sensitivity analyses of the key secondary endpoint confirm these results. The treatment difference between the aripiprazole (low and high doses) and placebo groups was statistically significant at all-time points in the trial and was observed at Week 1. The separation in the treatment difference continued to Week 2 and increased from there through Week 8. The treatment effect of the low- and high-dose aripiprazole groups was comparable at each time point in the trial.

Other secondary efficacy endpoints were the mean change from baseline to endpoint in Total YGTSS Score; mean change from baseline to endpoint in CGI-TS Severity Score; response rates (clinical response was defined as > 25% improvement from baseline to endpoint in the YGTSS TTS or a CGI-TS Change Score of 1 [very much improved] or 2 [much improved] at endpoint); and treatment discontinuation rates. Results of the Total YGTSS Score and the CGI-TS Severity Score also corroborated the primary efficacy results. The treatment difference between the low-dose aripiprazole and placebo groups for Total YGTSS Score (-13.26) and CGI-TS Severity Score (-0.80) at Week 8 was statistically significant, p = 0.0017 and p = 0.0010, respectively. The treatment difference between the high-dose aripiprazole and placebo groups for Total YGTSS Score (-19.37) and CGI-TS Severity Score (-0.92) at Week 8 was statistically significant, p < 0.0001 and p = 0.0002, respectively.

The response ratio (95% CI) (response ratio > 1 favours aripiprazole) using observed case (OC) data at Week 8 in the low- and high-dose aripiprazole groups, versus the placebo group, was 1.36 (0.98, 1.88) and 1.61 (1.20, 2.16), respectively. The response ratio for the low-dose aripiprazole group compared with the placebo group was not statistically significant; the response ratio for the high-dose aripiprazole group compared with the placebo group was statistically significant (p = 0.0014). Response was observed as early as Week 1 in both aripiprazole groups (for OC) and, except for the low-dose aripiprazole group at Week 8, was maintained throughout the trial.

Trial 031-KOA-0703

Primary endpoint

The primary endpoint was mean change of total Tic scores in K-YGTSS from randomisation (Visit 2) to the final visit at Week 10 (Visit 7). For the intention to treat (ITT) analysis the mean total Tic score was decreased from 29.48 (±5.60) at baseline to 19.86 (±9.54) at Visit 7 for the placebo arm, showing a decrease by -9.62 (±8.83). For aripiprazole, the mean total Tic score showed a greater decrease then placebo, changing from 28.34 (±5.51) at baseline to 13.55 (±9.12) at Visit 7, a decrease by -g14.97 (±8.42). The difference in the change from baseline to Visit 7 between the treatment groups was statistically significant (p=0.0196). The full analysis set (FAS) analysis showed identical results with the ITT analysis, other than a small difference in the summary statistics of baseline measurement in the aripiprazole group, due to the ITT data set having only one extra subject compared to the FAS, who was randomised but withdrawn prior to the study drug administration and for who post-administration efficacy data were not available. For the per protocol (PP) analysis the mean total Tic score was 28.19 (±5.72) at baseline and 17.24 (±7.44) at Visit 7 for placebo, showing a decrease by -10.95 (±7.89). For aripiprazole, the mean total Tic score showed a greater decrease than for placebo, changing from 28.35 (±4.65) at baseline to13.87 (±7.27) at Visit 7, a decrease by -14.48 (±7.76)]. However, the difference in the change from baseline to Visit 7 between treatment groups was not statistically significant. One possible reason for this difference in statistical

significance may be the exclusion of subjects from the PP population, who had shown a poor response while taking placebo. In addition, the same analysis was performed on the change from baseline to each visit (Visit 3 to 6) and the significance of the change from baseline to each visit in each treatment group was also assessed. ANCOVA was carried out on the difference in change from baseline to Visit 7 with age group, study site and baseline value as covariates.

Table: Analysis of Change from Baseline to Week 10 in K-YGTSS TTS for Trial 031-KOA-0703, LOCF)

						95% CI		
Analysis/ Treatment Group	**N[a]**	**Baseline Mean**	**Mean**	**Mean SE**	**Estimated Treatment Effect**	**Lower Limit**	**Lower Limit**	**P-value**
LOCF[c]								
Aripiprazole	31	28.3	−14.97	8.42	−5.35	-	-	0.0196
Placebo	29	29.5	−9.62	8.83				

CI = confidence interval; SE = standard error.

Note: TTS ranges from 0 to 50 with higher score for more severe symptoms (greater reduction from baseline for greater improvement).

[a]Protocol-specified LOCF analysis: number of subjects with baseline and at least one post-baseline measurement of the given variable for LOCF analysis. .

[c]Missing data imputed using LOCF analysis. P-value is computed from 2-sample t-test.

Source: CSR 031-KOA-0703 Table 10.12; m5\datasets\ise\analysis\programs\ eff0703.sas, RUN: 02DEC2013 11:11.

Secondary endpoints

Secondary efficacy endpoints included the percent change of total Tic scores in K-YGTSS from randomisation to the final visit, response rate in TS-CGI-I at the final visit, partial response rate in TS-CGI-I at the final visit, and mean change of Tourette's syndrome-Clinical Global Impression-Severity (TS-CGI-S) score. For the analysis of percent change of total Tic scores in K-YGTSS from randomisation (Visit 2) to the final visit (Week 10, Visit 7) the mean percent change was -33.00% (±27.83) for placebo and -52.86% (±27.83) for aripiprazole. The difference between the treatment groups was statistically significant (p-=0.0077). The analysis of response rate (percentage of subjects with score 1 or 2) in TS-CGI-I at the final visit showed a higher response rate for aripiprazole, with 21 subjects (65.63%) in the aripiprazole group and 13 subjects (44.83%) in placebo group being responders. However, there was no statistically significant difference in the response rate between the treatment groups. For the analysis of partial response rate (percentage of subjects with score 3) in TS-CGI-I, aripiprazole showed a higher partial response rate as 6 subjects (18.75%) in the aripiprazole group and 4 subjects (13.79%) in the placebo group were partial responders. However, the difference in the response rate between the treatment groups was not statistically significant. For mean change of TS-CGI-S score from randomisation (Visit 2) to the final visit (Visit 7) a decrease, by -1.10 (±1.14) was seen in the placebo group. For the aripiprazole group, the decrease was greater, by -1.71 (±1.30). The difference in the change from baseline to Visit 7 between the treatment groups was statistically significant (p=0.0321).

Table: Key Efficacy Results for Phase 3 Placebo-controlled Trial 31-12-293 and Trial 031-KOA-0703 in Paediatric Subjects with Tourette's Disorder (ITT Samples)

Study/ Endpoint/ Treatment group	N[a]	Baseline Mean	LS Mean[b]	Estimated Treatment Effect[b]	P-value[b]
Trial 31-12-293					
Change from baseline in YGTSS TTS at Week 8					
Aripiprazole low-dose	42	29.3	−13.35	−6.26	0.0020
Aripiprazole high-dose	35	31.5	−16.94	−9.85	< 0.0001
Placebo	42	30.3	−7.09		
CGI-I at Week 8[c]					
Aripiprazole low-dose	42	-	2.12	−1.03	0.0001
Aripiprazole high-dose	35	-	2.13	−1.02	0.0002
Placebo	42	-	3.15		
Trial 031-KOA-0703					
Change from baseline in YGTSS TTS at Week10[c]					
Aripiprazole	29	28.1	−15.86	−4.63	0.0386
Placebo	25	28.8	−11.23		
CGI-I at Week 10[d]					
Aripiprazole	29	-	2.21	−0.61	0.0780
Placebo	25	-	2.82		

LS = least squares.

Note: TTS ranges from 0 to 50 with higher score for more severe symptoms (greater reduction from baseline for greater improvement).

Note: Scoring for the Korean version of the CGI-I ranges from 1 to 8, with a lower score indicating improvement.

[a]Number of subjects with baseline and a measurement of the given variable at Week 8 for Trial 31-12-293 and at Week 10 for Trial 031-KOA-0703 (Section 2.7.3.1.2.2).

[b]Individual trial analyses are derived from a repeated measures linear model with treatment, week, and treatment-by-week interaction as fixed categorical effects, the baseline value as a fixed covariate, and week as the time variable for repeated measures. Trial 31-12-293 also included region and weight group as fixed categorical effects.

[c]Results for the protocol-specified LOCF analysis are presented in Section 2.7.3.3.2.1.2.

[d]Baseline CGI-S score used for the baseline value.

Source: Table 2.7.3.3.2.1.1-1, Table 2.7.3.3.2.1.2-1, Table 2.7.3.3.2.2.1-1, and Table 2.7.3.3.2.2.2-1.

2.2.3 Discussion

Trial 31-12-293

Trial was powered to test for a 5-point difference in change from baseline of YGTSS TTS between placebo and any of the treatment groups (defined as clinically meaningful improvement). In Trial 31-12-293, the LS mean change from baseline to Week 8 in YGTSS TTS showed statistical significance for both low-dose (−13.35; p = 0.0020) and high-dose (−16.94; p < 0.0001) aripiprazole compared with placebo (−7.09). The difference in treatment effect observed as early as Week 1 was sustained through the course of the trial, with a statistically significant treatment difference in favour of aripiprazole for the high-dose group at each time-point, and for the low-dose group at each time-point except at Week 2. These data were derived from an MMRM linear model that assumes the mechanism of missing data is MAR. Results of both MNAR scenarios revealed that the method used to impute missing data did not change the overall conclusion of the primary analysis. The step-down dose sensitivity analysis performed according to the dose to which subjects were stepped down showed that the treatment effect for YGTSS TTS remained statistically significant for both low-dose (p = 0.0009) and high-dose (p < 0.0001) aripiprazole compared with placebo. Seven subjects were stepped down to the next lower dose than their randomized dose: 4 subjects randomized to receive

10 mg and 1 subject randomized to receive 20 mg in the high-dose aripiprazole group, and 1 subject each randomized to receive 5 or 10 mg in the low-dose aripiprazole group.

The primary and key secondary efficacy analyses demonstrated that both low- and high-dose aripiprazole are statistically superior to placebo in the treatment of tics associated with Tourette's disorder in children and adolescents (aged 7-17 years). The results of the other secondary efficacy analyses corroborate the primary efficacy results.

Trial 031-KOA-0703

For primary efficacy analysis, the ITT, FAS and PP analysis results showed that the total Tic score decreased by visit and the differences from baseline were statistically significant at all visits in both treatment groups (paired t-test). The mean decreases were greater for aripiprazole than for placebo at all visits, and of these, the treatment difference was significant at Visit 3 and 5, in the ITT and FAS analysis. The primary efficacy endpoint, mean change of total Tic scores in K-YGTSS, and two of the secondary efficacy endpoints (percent change of total Tic scores in K-YGTSS and mean change of TS-CGI-S score from randomisation to the final visit) showed a statistically significant difference between treatment groups, with aripiprazole being superior to placebo.

Overall efficacy conclusions

The population in both trials was small, particularly Trial 031-KOA-0703, and the primary efficacy endpoint of the "low dose" aripiprazole arm, was not significantly different from placebo. This "low dose" is equal to the minimum adult maintenance dose for schizophrenia, and therefore is not really a "low dose".

No controlled trials have been conducted to assess the long-term efficacy and/or tolerance effects of aripiprazole for the treatment of tics associated with TD in paediatric patients 6 to 17 years of age.

Clinical meaningfulness of the differences was not established *a priori* nor was discussed afterwards. It is worth of note that the placebo effect was about half of the average effect of both aripiprazole arms in trial 31-12-293 and even more significant on trial 031-KOA-0703. Moreover, the main endpoint did not truly assess improvement of disability caused by TD.

Another important aspect is the fact that both studies were very short in treatment duration, and there is no available follow up data. Considering that TD is a chronic disorder, there is no robust evidence on the maintenance of effect on TD. In this respect, the CHMP noted that the SmPC approved information for "Irritability associated with autistic disorder in paediatric patients" was based on more clinically significant data.

In conclusion, MAH did not provide sufficient evidence of clinical efficacy of aripiprazole for the treatment of TD to support the initial proposed SmPC wording for section 5.1. See further details in section 2.4.

2.3 Clinical Safety aspects

2.3.1 Methods – analysis of data submitted

The primary analysis of safety was performed on data for the individual TD trials (Trials 31-12-293, 031-KOA-0703, and 31-12-294.

For the purposes of this submission, a TEAE was defined as an AE that began after the start of IMP or an AE that continued from baseline (before dosing) and that became serious or drug-related; resulted in death; or led to discontinuation, interruption, or reduction of IMP. An AE with an unknown start date

was considered a TEAE. For completed trials, AEs with an onset more than 30 days after the last day of IMP were excluded from the summary tables.

Breslow-Day tests for homogeneity were conducted for Trial 31-12-293 on subgroups of subjects based on age, gender, and race for TEAEs with an incidence ≥ 5% in subjects receiving aripiprazole and ≥ 2 times the incidence in subjects receiving placebo. The incidence of AESIs was summarized for the TD trials. Searches of the AE databases for specified preferred terms according to the Medical Dictionary for Regulatory Activities (MedDRA), version 16.0, were conducted to identify subjects with AESIs in the following categories: EPS-related events, suicidality-related events, weight gain-related events, prolactin-related events, hyperglycemia- or diabetes-related events and lipid parameter-related events.

2.3.2 Results

Overall Extent of Exposure

In Trial 31-12-293, a total of 89 subjects were exposed to aripiprazole: 44 and 45 subjects in the low- and high-dose aripiprazole groups, respectively. The largest proportion of subjects in the low-dose aripiprazole group (52.3%) was exposed for 50 to 56 days, and in the high-dose aripiprazole group, the largest proportion (44.4%) was exposed for > 56 days (CSR 31-12-293 CT-7.2). During the 50- to 56-day interval, the average daily dose was 4.8 and 9.5 mg for the low- and high-weight subjects in the low-dose aripiprazole group, respectively, and 9.0 and 17.6 mg for the low- and high-weight subjects in the high-dose aripiprazole group, respectively.

In Trial 031-KOA-0703, a total of 32 subjects were exposed to aripiprazole. The mean total duration of aripiprazole administration was 68.6 days, and the mean average daily dose of aripiprazole was 6.5 mg.

Deaths

No deaths have been reported during the two trials included in this submission.

Use in Pregnancy and Lactation

No pregnancies were reported in subjects the two clinical trials included in this submission.

2.3.2.1 Rates of AEs, SAEs, and Discontinuation of Therapy

Trial 31-12-293

A total of 133 subjects were included in the safety analysis: 44, 45 and 44 subjects in the low dose aripiprazole, high dose aripiprazole and placebo groups, respectively. The largest proportion of subjects in the low dose (52.3%) and high dose (44.4%) aripiprazole groups was exposed for 50 to 56 days and > 56 days, respectively. In the low and high dose aripiprazole groups, 43.2% and 44.4% of subjects, respectively, were exposed to aripiprazole for ≥ 8 weeks (i.e., ≥ 56 days). No subject in the trial received > 30 mg/day of aripiprazole.

No serious treatment-emergent adverse event (TEAEs) were reported. Discontinuation of trial medication due to a TEAE occurred in 9 subjects: 1 subject (2.3%) each, in the low dose aripiprazole and placebo groups and 7 subjects (15.6%) in the high dose aripiprazole group (Subject 530S3094 in the low dose [5 mg] aripiprazole group was discontinued trial medication due to severe somnambulism, but completed the trial). The trial completion rate was 95.5% in the low dose aripiprazole, 77.8% in the high dose aripiprazole, and 95.5% in the placebo groups. The discontinuation ratio was statistically significant for the high dose aripiprazole (22.2%) group

compared with the placebo group, due predominantly to the discontinuation rate of subjects who weighed < 50 kg and received aripiprazole 10 mg.

The overall incidence of TEAEs in the low and high dose aripiprazole groups was 65.9% and 75.6%, respectively, and 40.9% in the placebo group. The most frequently reported TEAEs that occurred in the low and high dose aripiprazole groups (with an incidence of ≥ 5% in both aripiprazole groups) were sedation (18.2% and 8.9%, respectively), somnolence (11.4% and 15.6%, respectively), increased appetite (9.1% and 6.7%, respectively), fatigue (6.8% and 15.6%), and headache, nasopharyngitis, and nausea (6.8% and 8.9%, respectively, each).

In general, TEAEs with an incidence of ≥ 5% in either aripiprazole group were experienced by a greater proportion of subjects who weighed < 50 kg than subjects who weighed ≥ 50 kg. In the low dose aripiprazole group, the exceptions were sedation and somnolence in < 50 kg subjects (14.3% and 10.7%, respectively) versus ≥ 50 kg subjects (25.0% and 12.5%, respectively). In the high dose aripiprazole group, the exceptions were akathisia and headache in < 50 kg subjects (3.3% and 6.7%, respectively) versus ≥ 50 kg subjects (13.3% for each). Most TEAEs were mild or moderate in intensity in the aripiprazole and placebo groups. There was 1 severe TEAE of somnambulism in the low dose aripiprazole group; 4 severe TEAEs of lethargy, sedation, somnolence, and insomnia in the high dose aripiprazole group; and no severe TEAEs reported in the placebo group. TEAEs considered by the investigator as potentially causally related to trial medication were reported for 20 (45.5%), 28 (62.2%), and 10 (22.7%) subjects in the low and high dose aripiprazole and placebo groups, respectively.

There were 1 (2.3%), 6 (13.3%), and no subjects in the low and high dose aripiprazole and placebo groups, respectively, who experienced extrapyramidal symptoms (EPS) related TEAEs. EPS rating scales (SARS (Simpson-Angus Rating Scale), BARS (Barnes-Akathisia Rating Scale), and Abnormal Involuntary Movement Scale (AIMS)) were assessed at baseline before dosing and at Weeks 1, 2, 4, 6 and 8. The treatment difference was statistically significant only between the high dose aripiprazole and placebo groups for the EPS rating scales of SAS (p = 0.0357) and AIMS (p = 0.0382).

There were no TEAEs related to prolactin, hyperglycaemia and diabetes, lipid parameters, or overdose.

While 2 subjects noted emergent suicidal ideation and 4 subjects had worsening suicidal ideation per responses to the C SSRS, no suicidal behaviour or ideation with a specific plan was observed and no suicide related adverse events (AEs) were reported. Weight gain-related TEAEs in the low- and high-dose aripiprazole and placebo groups were reported for 5 of 44 subjects (11.4%), 3 of 45 subjects (6.7%), and 1 of 44 subjects (2.3%), respectively. Potentially clinically relevant weight abnormalities (defined as a change of ≥ 7% from baseline) were seen at a higher incidence in the low-dose aripiprazole group (8/44 subjects; 18.2%) than in the high-dose aripiprazole and placebo groups (4/45 subjects; 9.3% and 4/44 subjects; 9.1%, respectively).

Additional scales were used to measure any increase in attention deficit/hyperactivity disorder (ADHD) Inattentive and ADHD Hyperactive/Impulsive symptoms, obsessive compulsive symptoms, oppositional defiant symptoms, depression, and anxiety symptoms. These included the Swanson, Nolan, and Pelham IV (SNAP IV) Rating Scale, Children's Yale Brown Obsessive Compulsive Scale (CY BOCS), Children's Depression Rating Scale Revised (CDRS R), and Paediatric Anxiety Rating Scale (PARS). No statistically significant difference was observed between the aripiprazole (low and high doses) and placebo groups, except on the SNAP IV, where high dose aripiprazole showed significant improvement over placebo in inattention subscale score (p = 0.0027), hyperactivity/impulsivity subscale score (p = 0.0352), and attention deficit disorder (ADD)/ADHD subscale total score (p = 0.0048).

Trial 031-KOA-0703

A total of 60 subjects were included in the safety analysis; 28 in the placebo group and 32 in the aripiprazole group. Extent of drug exposure was estimated by adding the amount of drug administration of all visits. The mean total amount of study medication taken during the study was 530.86 mg (±239.31) for placebo and 455.94 mg (±220.39) for aripiprazole, with no statistically significant difference between the treatment groups. The mean total duration of study drug administration was also not significantly different between treatment groups (63.75 days (±19.09) for placebo and 68.63 days (±10.02) for aripiprazole). No subjects withdrew from the study owing to TEAEs.

No deaths or suicidal ideation events were reported. All TEAEs were mild or moderate in severity, with no severe TEAEs being reported. TEAEs were experienced by 20 subjects (71.43%, 57 events) out of the 28 in the placebo group and 24 subjects (75.00%, 56 events) out of the 32 in the aripiprazole group, demonstrating no difference in the incidence rate between the treatment groups. However, one subject (Subject 003-0009) experienced an SAE of hydrocephalus during the screening period. The most common TEAEs reported at an incidence rate of ≥ 5% were akathisia (4/ 28 subjects, 14.29%) and dizziness (4/ 28 subjects, 14.29%) in the placebo group, and nausea (6/ 32 subjects, 18.75%) and headache (5/ 32 subjects, 15.63%) followed by sedation (4/ 32 subjects, 12.50%), somnolence (4/ 32 subjects, 12.50%) and nasopharyngitis (4/ 32 subjects, 12.50%) in the aripiprazole group. Seven TEAEs in the placebo group and 4 TEAEs in the aripiprazole group were moderate, and the rest of TEAEs were mild.

No SAEs were reported during randomised treatment and there were no other significant adverse events, including AEs that lead to withdrawal from the study.

EPS-related side effects were evaluated with the SARS, BARS, and AIMS scales. There was no significant difference between aripiprazole and placebo groups in mean change from baseline to Week 10 (Visit 7) in total SARS, BARS and AIMS scores. Each SARS, BARS and AIMS score item was also analysed by visit. No statistical significance was detected for change from baseline to each visit and for difference in these changes between the aripiprazole and placebo groups.

Treatment-emergent EPS and EPS related TEAEs were reported in 7 placebo and 5 aripiprazole treated patients. Akathisia occurred in 4 (14.29%) subjects in the placebo group and 1 (3.13%) subject in the aripiprazole group. Extrapyramidal disorder occurred in 1 (3.57%) subject in the placebo group and 3 (9.38%) subjects in the aripiprazole group. Dystonia occurred in 2 (7.14%) placebo subjects and bradykinesia in 1 (3.13%) aripiprazole subject. No weight gain or loss were reported. Notwithstanding, Aripiprazole-treated subjects had a mean (± SD) increase from baseline in body weight of 1.62 ± 2.02 kg, while subjects in the placebo group had a mean (± SD) increase from baseline of 0.20 ± 1.84 kg (CSR 031-KOA-0703 Table 13.47). Nine of 32 subjects (28.1%) in the aripiprazole group and 2 of 28 subjects (7.1%) in the placebo group had potentially clinically relevant weight gain (≥ 7% change from baseline) at Week 10; however, the differences between treatment groups were not statistically significant.

2.3.2.2 Laboratory Assessments, Vital Signs, ECG

Trial 31-12-293

No significant findings were shown in clinical laboratory values, vital signs and ECG parameters The incidence of potentially clinically relevant laboratory values was similar across the low and high dose aripiprazole and placebo groups, except for creatine phosphokinase (CPK) and fasting glucose, which were elevated in 2 subjects each in the low and high dose aripiprazole groups versus no subjects in the placebo group. No clinically relevant mean changes were observed in the insulin or fasting insulin results.

The mean change from baseline at Week 8 in the prolactin test results for the low and high dose aripiprazole male groups (5.82 [± 7.25] and 4.32 [± 6.84], respectively) and female groups (15.58 [± 23.23] and 5.40 [± 7.78], respectively) was greater than for the placebo group males (1.48 [± 7.88]) and females (0.23 [± 4.66]). The mean change from baseline at last visit in the prolactin test results for the low dose and high dose aripiprazole male groups (5.57 [± 7.29] and 4.22 [± 6.38], respectively) and female groups (12.31 [± 23.40] and 5.03 [± 7.43], respectively) was greater than for the placebo group males (1.37 [± 7.66]) and females (0.23 [± 4.66]).

One subject had an increase from baseline in QTc of > 60 msec or a QTc value of > 500 msec. One high dose aripiprazole (10mg) subject had an ECG related TEAE that led to discontinuation of trial medication at the investigators discretion and three subjects had potentially clinically relevant ECG abnormalities during the trial (one low dose aripiprazole (5mg) and two high dose aripiprazole (20mg)).

Trial 031-KOA-0703

There were no apparent safety issues observed with the laboratory test, vital signs, or ECG results. No clinically relevant mean changes were observed in the insulin or fasting insulin results. No clinically meaningful trends were observed for any of the potentially clinically significant laboratory test abnormalities. Any reported abnormalities in laboratory tests, vital signs, and ECG parameters all appeared to be isolated findings.

Serum prolactin showed a statistically significant mean change, by -5.85 (±4.93) (Median = -4.45, p<0.0001) in the aripiprazole group. This change was significantly different (p<0.0001) from that in placebo group (Mean change = -0.10 (±3.24), Median = 0.10).

2.3.2.3 Laboratory Measurements of Special Interest

Trial 31-12-293

No clinically meaningful changes from baseline were observed in any laboratory measurements of special interest such as fasting blood levels for triglycerides, high-density lipoprotein (cholesterol) (HDL-C), glucose and systolic and diastolic blood pressure.

With a potentially clinically relevant weight abnormality defined as a change > 7%, the incidence of a weight gain abnormality was higher in the low dose aripiprazole group (8 subjects [18.2%]) than in the high dose aripiprazole and placebo groups (4 subjects each [9.3% and 9.1%, respectively]). The incidence of weight gain related TEAEs, which included events of weight increased and increased appetite was higher in the low dose aripiprazole group (5 [11.4%] subjects) than in the high dose aripiprazole group (3 [6.7%] subjects) and the placebo group (1 [2.3%] subjects). Two low dose aripiprazole (one 10 mg, one 5 mg) subjects had a TEAE of weight increased during the trial.

Trial 031-KOA-0703

No clinically meaningful changes from baseline were observed in any laboratory measurements of special interest such as fasting blood levels for triglycerides, HDL-C, glucose and systolic and diastolic blood pressure.

Body weight showed a statistically significant mean change, by 1.62kg (±2.02) (p = 0.0001) in the aripiprazole group. This change was significantly different (p = 0.0102) from that in placebo group (Mean change = 0.20 kg (±1.84), p = 0.6070). BMI showed a statistically significant mean change, by 0.45 kg/m2 (±0.86) (p-value = 0.0079) in aripiprazole group. This change was significantly different (p-value = 0.0243,) from that in placebo group (Mean change = -0.09 kg/m2 [±0.85]). Waist circumference also showed a statistically significant mean change, by 1.83 cm (±3.80) (p = 0.0093) in aripiprazole group. This change was found significantly different (p = 0.0293) from that in placebo group (Mean change = -0.07 cm [±2.90]). Considering baseline and final BMI, the weight

gain is not considered excessive, and the weight gain may be seen as a natural consequence of symptom relief from Tic disorders or Tourette's disorder.

2.3.3 Discussion

Aripiprazole is known to cause adverse events (AEs), and the most expected in the paediatric age range are EPS, weight gain, and somnolence. It was fairly well studied in paediatric bipolar type I disorder, which shares common comorbidities like Attention Deficit Hyperactivity Disorder (ADHD), and in these children, some of the adverse events were cumulatively more evident after the first weeks of treatment. Weight gain threshold of >7% increase over baseline must take enough time to be attained, and short trials fail to identify this. Of note, the indication "for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents" was adopted for children aged 13 years and older due to safety issues in children between 10 and 12 years of age.

Delayed onset adverse events, such as neuroleptic tardive syndrome cannot be identified on such short trials. This is particularly important since TD may be a form of tardive disease, and thus the patient may improve in the first months or years of treatment, and then worse tics again either in the context of worsening of the primary disease or as a new tardive disorder with similar symptoms.

TD is a spectrum, which range from minor non incapacitating tics to motor and socially disabling tics. Safety issues must thus be weighed against efficacy through the entire range of disease severity. It is known that different disease populations have different AE profile. With these very short term trials the profile of AEs in TD cannot be identified. Adverse events were only followed up for 30 days after IMP stops. Therefore there is no data on medium term or delayed adverse events. Events with a cumulative effect such as weight gain were not adequately followed in order to properly weigh their safety value.

2.4 Changes to the Product Information

The MAH initially proposed the following changes to the Product Information (PI) (deleted text= strikethrough, new text= underlined):

Section 4.2

Tics associated with Tourette's disorder: the safety and efficacy of ABILIFY in children and adolescents 6 to 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.

Section 5.1

Tics associated with Tourette's disorder in paediatric patients (see section 4.2)

The efficacy of aripiprazole in the treatment of Tourette's disorder was established in one 8-week (7 to 17 years of age) and one 10-week (6 to 18 years of age), placebo-controlled trials in paediatric patients. In the 8-week placebo-controlled trial, children and adolescents with Tourette's disorder (n=133), received daily doses of placebo or aripiprazole based on weight. Patients < 50 kg started at 2 mg/day with a target dose of 5 mg/day after 2 days, and were allowed to increase to 10 mg/day if they did not achieve optimal control of tics at or after day 7. Patients weighing ≥ 50 kg, started at 2 mg/day increased to 5 mg/day after 2 days, with a subsequent increase to a target dose of 10 mg/day at day 7 and were allowed weekly increases of 5 mg/day up to 20 mg/day for patients who did not achieve optimal control of tics. Aripiprazole demonstrated statistically significantly improved scores on total tic score (TTS) of the Yale Global Tic Severity Scale (YGTSS) change from baseline to Week 8 and on the CGI-I scale compared with placebo in patients with a minimum total tic score on the YGTSS scale greater than 20 at baseline. In the 10-week, placebo-controlled trial in children and adolescents

with Tourette's disorder (n=61), aged 6 to 18 years, patients received daily doses of placebo or aripiprazole, starting at 2 mg/day with increases allowed up to 20 mg/day based on clinical response. Aripiprazole demonstrated significantly improved scores on the YGTSS scale compared with placebo. The mean daily dose of aripiprazole at the end of 10-week treatment was 6.54 mg/day.

However, the clinical relevance of these findings has not been established. The safety profile for these two studies remains unchanged compared to approved paediatric indications.

During the procedure, the CHMP concluded that there was insufficient evidence to support the proposed wording of the SmPC update for section 5.1 for the following reasons:

- TD is a broad spectrum syndrome, with some patients experiencing simple and non-bothersome tics with no QoL impact, while on the other end of the spectrum patients develop a severe and disabling form of disorder.

- TD may significantly change in symptom intensity in the individual patient. Tics are known to have a bimodal distribution, peaking around 8-10 years of age, and with a second less striking peak in the 60's. Moreover, tic severity also changes with emotional and environmental stress, to a significant extent: children with tics suffer less when on holidays. Therefore trials with up to 10 week duration may be considered too short to draw conclusions on efficacy.

- The tools used to assess TD were adequate, but the Total YGTSS score (Total Yale Global Tic Severity Scale Score (Total Tic Severity Score + Impairment) was not the primary endpoint. In fact, only the Total Tic Severity Score was used, and therefore the consequence of Tics upon impairment (which is what is the most important) was not described. Also, the minimum value of change with clinical significance was not set a priori for this score, and thus the magnitude of effect (which was not paramount when compared to placebo effect) may not be clinically relevant, particularly considering the above aspects of the disease.

- Aripiprazole is known to cause adverse events (AEs), and the most expected in this age range are EPS, weight gain, and somnolence. It was fairly well studied in paediatric bipolar type I disorder, which shares common comorbidities like Attention Deficit Hyperactivity Disorder (ADHD), and in these children some of the adverse events were cumulatively more evident after the first weeks of treatment. Weight gain threshold of >7% increase over baseline must take enough time to be attained, and short trials fail to identify this. Of note, the indication "for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents" was adopted for children aged 13 years and older due to safety issues in children between 10 and 12 years of age.

- Delayed onset adverse events, such as neuroleptic tardive syndrome cannot be identified on such short trials. This is particularly important since Tourette may be a form of tardive disease, and thus the patient may improve in the first months or years of treatment, and then worse tics again either in the context of worsening of the primary disease or as a new tardive disorder with similar symptoms.

The CHMP therefore requested further amendments to the PI (section 5.1) that were agreed by the MAH.

The final recommended wording was as follows:

Section 4.2

Tics associated with Tourette's disorder: the safety and efficacy of ABILIFY in children and adolescents 6 to 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.

Section 5.1

Tics associated with Tourette's disorder in paediatric patients (see section 4.2)

The efficacy of aripiprazole was studied in paediatric subjects with Tourette's disorder (aripiprazole: n = 99, placebo: n = 44) in a randomised, double-blind, placebo controlled, 8 week study using a fixed dose weight-based treatment group design over the dose range of 5 mg/day to 20 mg/day and a starting dose of 2 mg. Patients were 7 - 17 years of age and presented an average score of 30 on Total Tic Score on the Yale Global Tic Severity Scale (TTS-YGTSS) at baseline. Aripiprazole showed an improvement on TTS-YGTSS change from baseline to Week 8 of 13.35, for the low dose group (5 mg or 10 mg) and 16.94 for the high dose group (10 mg or 20 mg) as compared with an improvement of 7.09 in the placebo group.

The efficacy of aripiprazole in paediatric subjects with Tourette's syndrome (aripiprazole: n = 32, placebo: n = 29) was also evaluated over a flexible dose range of 2 mg/day to 20 mg/day and a starting dose of 2 mg, in a 10 week, randomised, double blind, placebo-controlled study conducted in Korea. Patients were 6 - 18 years and presented an average score of 29 on TTS-YGTSS at baseline. Aripiprazole group showed an improvement of 14.97 on TTS-YGTSS change from baseline to Week 10 as compared with an improvement of 9.62 in the placebo group.

In both of these short term trials, the clinical relevance of the efficacy findings has not been established, considering the magnitude of treatment effect compared to the large placebo effect and the unclear effects regarding psycho-social functioning. No long term data are available with regard to the efficacy and the safety of aripiprazole in this fluctuating disorder.

3. Overall conclusion and impact on the benefit/risk balance

TD is a disorder with a broad spectrum of symptoms and disability. Its continuously modifying clinical expression is particularly challenging for the treating physician, but also for clinical investigation and the attempt to design adequate clinical trials to address the subject.

Reference literature frequently describes antipsychotics as agents to treat motor symptoms of TD, but most agents do not have a specific indication on TD or tics. Antipsychotics as a group are broadly described as possessing an effect of sufficient magnitude to be used in TD, but there are no specific recommendations for titration or drug adjustment, nor evidence of maintenance of effect.

Adverse events of antipsychotics are also of particular concern, particularly when to be used on paediatric TD population, who are not as severely disabled as schizophrenic or bipolar adolescents, and most important are younger than the pediatric groups for whom aripiprazole has an indication.

The clinical trials of aripiprazole in children with TD provided useful data for healthcare professionals, for which no atypical antipsychotic agent is approved. The CHMP concluded that the addition of such information in the SmPC was considered acceptable, taking into consideration the knowledge about the disease, the limited efficacy data of aripiprazole on TD - particularly regarding maintenance data and the lack of long term safety data, especially for a sustained treatment.

The benefit-risk balance of Abilify remains positive in the authorised indications.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SPC) to include information related to studies 31-12-293 and 031-KOA-0703 conducted in patients (6-18 years) with Tourette's disorder (TD).

The requested variation proposed amendments to the Summary of Product Characteristics.