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Abilify

(aripiprazole)

Procedure No. EMEA/H/C/000471/P46-061

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

I. ASSESSMENT

Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:
results of the final clinical study report (CSR) for Study Number 31-09-266: A long-term, multicentre, randomised, double-blind, placebo-controlled Study to evaluate the efficacy, safety, and tolerability of Aripiprazole (OPC-14597) as Maintenance Treatment in Adolescent Patients with Schizophrenia
This report discusses the results of Trial 31-09-266 that addresses the requirements of the Paediatric Investigation Plan (EMEA-000235-PIP02-10-M02) for the treatment of schizophrenia in patients 13 to 17 years of age in order to demonstrate the maintenance of effects.
The trial was conducted in compliance with Good Clinical Practice (GCP), the sponsor's standard operating procedures (SOPs), and ethical principles for the protection of human research subjects that have their origins in the Declaration of Helsinki.

Product Development Rationale

Aripiprazole is an atypical antipsychotic that is approved via centralised procedure in the European Union (EU) as different pharmaceutical forms in multiple indications (Abilify - EMEA/H/C/000471). In the EU aripiprazole is approved for:

- Treatment of schizophrenia in adults and adolescents (ages 15 years and older) (oral formulations)
- Treatment of moderate to severe manic episodes in bipolar I disorder in adults (oral formulations)
- Treatment up to 12 weeks of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 years and older (oral formulations)
- Prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (oral formulations)
- 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 (immediate-release IM formulation)
- Maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole (prolonged-release suspension for injection formulation, Abilify Maintena, EMEA/H/C/002755)

In the United States (US) aripiprazole is approved for:

- Treatment of schizophrenia in adults (oral formulations)
- Treatment of schizophrenia in adolescents (ages 13 – 17 years) (oral formulations)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate in adults and paediatric patients (ages 10 – 17 years) (oral formulations)
- Maintenance treatment of bipolar I disorder both as monotherapy and as an adjunct to either lithium or valproate in adults (oral formulations)
- Adjunctive treatment of major depressive disorder (MDD) in adults (oral formulations)
- Treatment of irritability associated with autistic disorder in paediatric patients (ages 6 – 17 years) (oral formulations)
- Acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults (immediate-release IM formulation)
- Maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole (prolonged-release suspension for injection formulation)

Aripiprazole is also approved in a variety of indications in other countries, including the treatment of Tourette's disorder in the Republic of Korea (ages 6 – 18 years).

Methodology

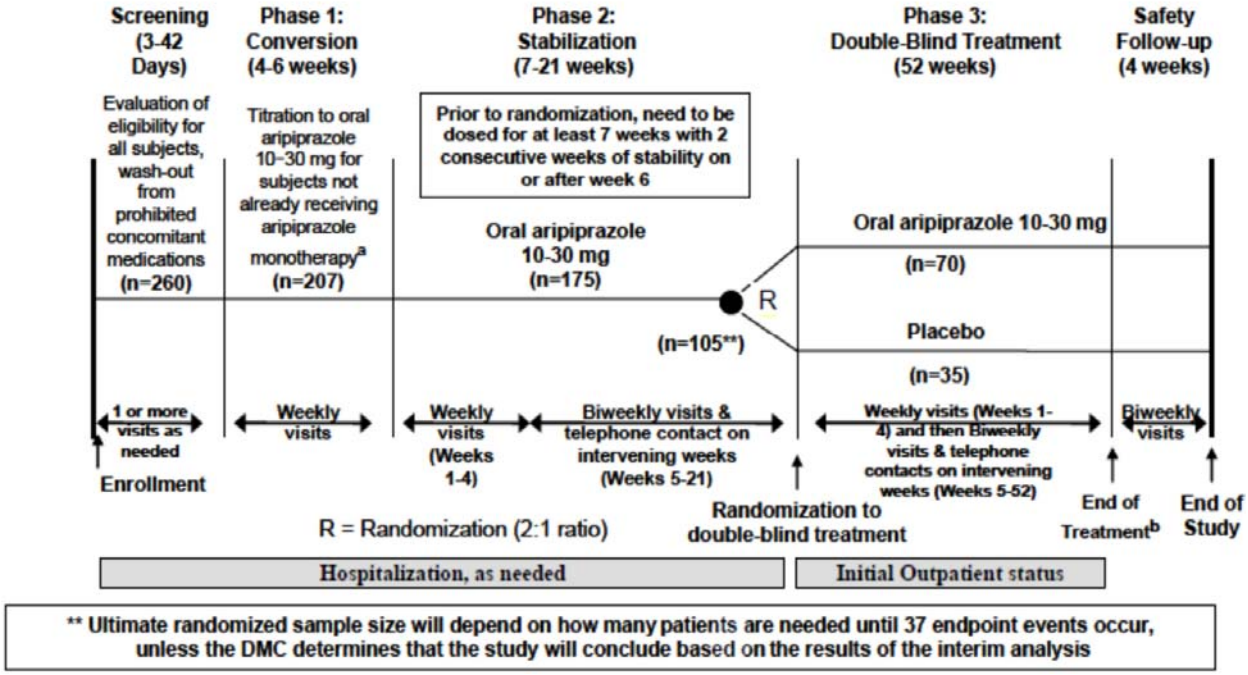
Trial 31-09-266 was a phase 3 long-term multicentre, randomised, double-blind, placebo controlled study to evaluate the efficacy, safety and tolerability of aripiprazole as maintenance treatment in adolescent patients aged 13 to 17 years with schizophrenia. Subjects were male or female adolescents aged 13 to 17 years, inclusive, at the time of informed consent/assent, with a current diagnosis or symptoms of schizophrenia for at least 6 months according to Diagnostic and Statistical Manual of Mental disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. Subjects were required to be in good physical health as determined by medical history, clinical laboratory tests, electrocardiogram (ECG), and physical examinations.

In the EU, aripiprazole is approved for subjects aged 15 to 17 years old, and in the US, it is approved for subjects aged 13 to 17 years old. The enrolment in the trial was monitored during the conduct of the trial to ensure that only subjects aged 13 to 14 years old were enrolled.

Trial 31-09-266 consisted of a screening period, three treatment phases (conversion, stabilisation, and double-blind maintenance), and a follow-up period:

- Screening phase of 3 to 42 days, to assess eligibility and allow washout of prohibited medications, followed by
- 4 to 6 weeks conversion phase, during which subjects were cross-titrated from other antipsychotic(s) to oral aripiprazole, followed by
- 7 weeks to 21 weeks stabilisation phase to stabilise subjects on an aripiprazole dose, within the approved dose range, followed by
- 52-week double blind, placebo-controlled maintenance phase, followed by
- Open-label safety trial of aripiprazole (Protocol 31-09-267)

Figure: Trial Design Scheme



Subjects could either have been outpatients or inpatients between screening and through the time they reached stabilisation, however subjects had to have been outpatients at the beginning of the double-blind maintenance phase.

During the 4 to 6 weeks conversion phase, subjects were cross-titrated from other antipsychotic(s) to oral aripiprazole monotherapy. Any subject who met the eligibility criteria and was receiving oral

aripiprazole monotherapy at a minimum dose of 10 to 30 mg/day at the time of screening entered directly into the stabilization phase. Subjects who met the eligibility criteria and were receiving lower doses of aripiprazole monotherapy between ≥ 5 mg/day and < 10 mg/day at the time of screening, bypassed the conversion phase and continued on the same dose at the beginning of the stabilisation phase, but had to achieve a minimum target dose of 10 mg/day by Day 6 of the stabilisation phase.

Subjects who were currently receiving aripiprazole monotherapy at a dose of < 5 mg/day were required to enter the conversion phase. The aim of the conversion phase was to achieve aripiprazole oral monotherapy at a minimum target dose of 10 mg/day at Week 4, and no later than Week 6, before entering the stabilisation phase. However, higher starting doses were acceptable (up to 30 mg/day), based on investigator judgment and subject's clinical need.

During the stabilisation phase, subjects were stabilised on aripiprazole within the dose range of 10 mg/day to 30 mg/day over a minimum of 7 weeks and a maximum of 21 weeks. Based on clinical judgment with regard to tolerability issues, the investigator was allowed to reduce the subject's aripiprazole dose, but to no less than 10 mg/day. If a dose reduction to 5 mg/day was required after Day 6 in the stabilisation phase, the subject was discontinued from the trial. Eligible subjects were allowed to bypass the conversion phase and enter the stabilisation phase directly if:

1) the subject recently had been without antipsychotic treatment (for no more than 3 weeks) prior to screening and the subject had a history of relapse and/or exacerbation of symptoms when not receiving antipsychotic treatment, or
2) if the subject was being treated with oral aripiprazole monotherapy between 10 mg/day to 30 mg/day or
3) if the subject was treated with a lower dose of branded aripiprazole between ≥ 5 mg/day and < 10 mg/day, but achieved a minimum target dose of 10 mg/day by Day 6 of the stabilisation phase.

Subjects were assessed for stability beginning at Week 6 of the stabilisation phase. Stability in the stabilisation phase was achieved after 2 consecutive weekly assessments, starting no sooner than Week 6 at which the subject met predefined stability criteria. Consequently, at any time between Weeks 7 and 21, subjects meeting stability criteria at 2 consecutive weekly assessments were randomised and entered the double-blind maintenance phase. In order to enter the double-blind maintenance phase, all subjects must have been on a minimum daily dose of 10 mg aripiprazole when the stability criteria were met.

Stability was defined as fulfilment of all of the following criteria at 2 consecutive weekly assessments starting at Week 6:

1) Outpatient status AND
2) (PANSS) Total Score ≤ 80 AND
3) Lack of specific psychotic symptoms on the PANSS as measured by a score of ≤ 4 on each of the following items (possible scores of 1 to 7 for each item):
   - Conceptual disorganization
   - Suspiciousness
   - Hallucinatory behaviour
   - Unusual thought content AND
4) A CGI-S (Clinical Global Impression of Severity) score ≤ 4 (moderately ill) AND
5) No current suicidal behaviour as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) (and an answer of "no" to Questions 4 and 5 on the suicidal ideation section of the C-SSRS) AND
6) No evidence of aggressive or violent behaviour that resulted in clinically, significant self-injury, injury to another person, or property damage, or inability to attend school due to this behaviour.

A period of up to 21 weeks was permitted to maximise the possibility of achieving the required duration of symptom stability. Assessments for stability continued until the subject could not meet the stability criteria at 2 consecutive weekly visits on or before Week 21. Any subject who had not met the stability criteria at Week 20 was withdrawn from the trial.

From the stabilisation phase, subjects were randomised in a 2:1 ratio to receive either aripiprazole 10 mg/day to 30 mg/day or placebo in a double-blind fashion, with double-blind treatment continuing for up to 52 week after randomisation. During the double-blind maintenance phase, outpatient subjects were evaluated weekly for the first 4 weeks and then every 2 weeks. Subjects reported condition was assessed via telephone in the weeks that fell between trial centre visits, with the option of bringing the subject back to the trial centre, if there were any concerns.
At all visits, subjects were evaluated for signs of exacerbation of psychotic symptoms/ impending relapse and subjects were withdrawn from the trial if any such signs were observed. Any subject withdrawn for "lack of efficacy" or "worsening of illness" during the double-blind maintenance phase had to meet at least 1 of the criteria for exacerbation of psychotic symptoms/impending relapse as defined in the trial protocol.
Subjects who completed the double-blind maintenance phase and those who discontinued from the trial due to impending relapse in the double-blind maintenance phase, or were withdrawn by the investigator for "lack of efficacy" or "worsening of illness" during the double-blind maintenance phase, and who met at least 1 of the protocol criteria for exacerbation of psychotic symptoms/impending relapse could enter an open-label safety trial of aripiprazole (Protocol 31-09-267). Subjects withdrawn from conversion or stabilisation phases prior to termination of the trial were not eligible for participation in this open-label trial. Subject who did not enter the open-label trial were followed up for safety/tolerability at visits 2 weeks (± 3 days) and 4 weeks (± 3 days) after the last trial visit. Follow-up treatment in the form of non-trial medication supplement was offered for up to 12 weeks.

The primary efficacy endpoint in the trial was the time from randomisation to exacerbation of psychotic symptoms/impending relapse in the double-blind maintenance phase. Impending relapse was defined as meeting any of the following 5 criteria:

1) A Clinical Global Impression of Improvement (CGI-I) score of ≥ 5 (minimally worse) AND
    - an increase in any of the following individual Positive and Negative Syndrome Scale (PANSS) items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) to a score > 4 with an absolute increase of ≥ 2 on that specific item since randomization OR
    - an increase in any of the following individual PANSS items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) to a score > 4 and an absolute increase of ≥ 4 on the combined 4 PANSS items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) since randomization OR
2) A CGI-I score of 6 or 7 (much or very much worse) OR
3) Hospitalization due to worsening of illness (including partial hospitalization programs), but excluding hospitalization for psychosocial reasons OR
4) Any suicidal behaviour or answers of "yes" to Questions 4 or 5 on the suicidal ideation section of the C-SSRS OR
5) Violent or aggressive behaviour resulting in clinically significant self-injury, injury to another person, or property damage or inability to attend school due to this behaviour.

In the double-blind maintenance phase the following **secondary efficacy variable** were compared between the aripiprazole treatment group and the placebo group at endpoint:

- Percentage of subjects meeting exacerbation of psychotic symptoms/impending relapse criteria
- Percentage of responders in each treatment group (i.e., response defined as meeting stability criteria)
- Percentage of subjects achieving remission, where remission is defined as a score of ≤ 3 on each of the following specific PANSS items, which was maintained for a period of 6 months: delusions (P1), unusual thought content (G9), hallucinatory behaviour (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6)
- Time to discontinuation for all causes

Other Endpoints are

Efficacy:

- Mean change from baseline to endpoint in PANSS Total Score
- Mean change from baseline to endpoint in CGI-S score
- Mean CGI-I score at endpoint
- Mean change from baseline to endpoint in PANSS positive and negative subscales
- Mean change from baseline to endpoint in CGAS

Safety:

- The frequency and severity of AEs, seriousness of AEs (clinical and laboratory), and discontinuation from trial due to AEs
- The frequency of symptom items for the NY-AACENT
- The frequency of side effects for the UKU Side Effects Rating Scale
- Analysis of potential suicide events recorded on the C-SSRS
- Mean change from baseline and incidence of clinically significant changes from baseline for clinical laboratory tests and urinalysis results (including fasting blood lipids and glucose, serum prolactin, insulin, haemoglobin A1c, and creatinine phosphokinase [CPK]), vital signs and ECG parameters. A central ECG service was utilized to review all ECGs in order to standardize interpretations for the safety analysis.
- Review of physical examination findings
- Baseline and post-baseline Tanner Staging
- Mean change from baseline of z-scores for height and body weight, mean changes of BMI, and waist circumference
- Mean change from baseline to endpoint on the AIMS, SAS, and BARS

Patient Population

A total of 201 subjects entered the trial, with 146 subjects randomised in the double-blind maintenance phase (98 subjects to aripiprazole, 48 subjects to placebo). Of the 201 subjects who entered the trial, 56 (27.9%) were between 13 and 14 years old and 145 (72.1%) were at least 15 years old. Of the 146 subjects randomised in the double-blind maintenance phase, 21 subjects completed the trial (15 aripiprazole, 6 placebo).

Of the 146 subjects randomised in the double-blind maintenance phase, 33 (22.6%) were between the age of 13 and 14 years and 113 (77.4%) were at least 15 years old. There were a larger number of male subjects than female subjects enrolled in the trial: 133 male subjects (66%) compared to 68 female subjects. Female subjects and subjects aged 13 to 15 years were considered to be adequately represented in the subject population. In the double-blind maintenance phase, there were 98 subjects (62 males (63%) and 36 females) in the aripiprazole group and 48 subjects (34 males (71%) and 14 females) in the placebo group. The majority of subjects were white or Asian and non-Hispanic or Latino.

The main reason for subject discontinuation from the trial was the sponsor terminating the trial (180 subjects [89.6%] total), which occurred after the 37th event of exacerbation of psychotic symptoms/impending relapse occurred as it is defined in the clinical study protocol. Subjects on the study at the time of study termination were offered to roll over to an open label study for up to one year. All subjects were analysed for safety and all subjects in the stabilization and double-blind maintenance phases were analysed for efficacy.
In general, baseline disease severity was comparable between treatment groups. The mean age of first diagnosis of schizophrenia for subjects was 13 years. There was a decrease in PANSS total score between the conversion phase n = 185 subjects (mean 86.9) and the double-blind maintenance phase where n = 146 subjects (mean 65.5 in aripiprazole group and 62.9 in placebo group). There was a decrease in mean CGI-S scores in the double-blind maintenance phase for both treatment groups (3.2 in aripiprazole group and 3.0 in placebo group) relative to the larger group treated in the conversion phase. The mean Children's Global Assessment Scale (CGAS) score increased in the double-blind maintenance phase in both treatment groups (60.9 in aripiprazole group and 66.1 in placebo group).

Results

Primary endpoint

Aripiprazole was superior to placebo as measured by time to exacerbation of psychotic symptoms/impending relapse, as derived from the Cox Proportional Hazard model (p = 0.0161). There was a statistically significant delay in time to exacerbation of psychotic symptoms/impending relapse for aripiprazole-treated subjects compared to placebo-treated subjects. The overall relapse rate was lower in the aripiprazole-treated subjects (19.39%) compared to placebo-treated subjects (37.50%). Sensitivity analyses for time to exacerbation of psychotic symptoms/impending relapse for multiple imputation approach confirmed the primary analysis results (all p-values under different situations less than 0.021). The sensitivity analysis for time to exacerbation of psychotic symptoms/impending relapse for discontinuations due to reasons other than sponsor discontinued the trial also supported the primary analysis (p = 0.0076).

Secondary endpoints

A greater proportion of subjects treated with placebo met at least one of the exacerbation of psychotic symptoms/impending relapse criteria compared to aripiprazole-treated subjects (p = 0.0181). All psychotic symptoms/impending relapse criteria were met by a higher incidence of placebo-treated subjects compared to aripiprazole-treated subjects with the exception of suicidal behaviour (0 of 48 subjects in the placebo group vs. 1 of 98 subjects in the aripiprazole group).
The difference in the percentage of aripiprazole-treated subjects who were responders at the last visit compared to placebo-treated subjects was not statistically significant (p = 0.0962). At the last visit, 76 of 98 (77.6%) aripiprazole-treated subjects were responders compared to 31 of 48 (64.6%) of placebo-treated subjects.
A statistically significant difference in the time to discontinuation prior to Day 378, for reasons other than sponsor terminated the trial, in the double-blind maintenance phase, was seen in the placebo subjects compared to aripiprazole subjects (p = 0.0076). The discontinuation rate for placebo-treated subjects was 47.92% compared to 25.51% for aripiprazole-treated subjects.

Other efficacy endpoints

In general, symptom stability was maintained in the aripiprazole group, as measured by lack of change in the PANSS total, positive, negative, CGI-I and CGI-S scores, and worsened in placebo. However, the differences in the adjusted mean changes from baseline, based on the last observation carried forward (LOCF) dataset, between aripiprazole- and placebo-treated subjects were not statistically significant. There was no notable change from baseline in the PANSS Total Score, based on the LOCF dataset, for aripiprazole-treated subjects during the double-blind maintenance. In contrast, the PANSS Total Score, based on the LOCF dataset, increased

(worsened) from baseline over the course of the double-blind maintenance for placebo-treated subjects. There was no notable change from baseline in the PANSS Positive Subscale Score or Negative Subscale Score by week, based on the LOCF or observed cases (OC) datasets, for either treatment group. However, differences were seen in the adjusted mean changes.
There was no notable change from baseline in the CGI-S Score based on the LOCF dataset for aripiprazole-treated subjects during the double-blind maintenance phase and a very slight increase for placebo-treated subjects. There was a statistically significant treatment difference seen in the mean CGI-I score, based on the LOCF dataset, for aripiprazole- vs placebo-treated subjects from Weeks 10 to 30 ($p \leq 0.0037$). Thus, aripiprazole-treated subjects fared slightly better, based on CGI-I score, than placebo-treated subjects. There was no mean change from baseline in the CGAS Score by week, based on the LOCF or OC datasets, for either treatment group. However, differences were seen in the adjusted mean changes.

Safety

Rates of AEs, SAEs, and Discontinuation of Therapy

Overall, during the stabilisation phase, the mean average daily dose (SD) was 18.4 mg (6.1) in the aripiprazole group and 17.1 mg (5.9) in the placebo group. In the double-blind maintenance phase, the mean average daily dose (SD) was 19.2 mg (6.7) in the aripiprazole group and 17.7 mg (6.6) in the placebo group.
Overall, in the double-blind maintenance phase, the mean number of days of aripiprazole exposure was 184.6 days in the aripiprazole group and 158.1 days in the placebo group, however it is important to mention that the study was designed to be early terminated after the 37th impending relapse event. The minimum number of days of aripiprazole exposure in the double-blind maintenance phase was 6 days and maximum was 371 days.
In the stabilization phase, a total of 183 (100.0%) subjects were treated with aripiprazole oral tablets. A total of 109 (59.6%) subjects reported treatment-emergent adverse events (TEAEs). Four (2.2%) subjects reported serious TEAEs and 4 (2.2%) subjects reported TEAEs that were considered severe in severity. Seven subjects (3.8%) discontinued trial medication due to AEs.
A total of 146 subjects were randomised in the double-blind maintenance phase (98 aripiprazole, 48 placebo). A total of 140 TEAEs were reported by 64 (65.3%) subjects in the aripiprazole group and 79 TEAEs reported by 33 (68.8%) subjects in the placebo group. The most frequently reported TEAE's were:

Table 2.5.5.1-1 Most frequent TEAEs

TEAE	**Aripiprazole**		**Placebo**	
	subject(s)	%	subject(s)	%
Schizophrenia	10	10.2	13	27.1
Insomnia	5	5.1	9	18.8
Psychotic disorder	9	9.2	5	10.4
Weight increased	8	8.2	5	10.5
Nasopharyngitis	7	7.1	1	2.1

Most TEAEs were mild or moderate in severity.
A total of 45 (45.9%) TEAEs considered by the investigator as potentially causally related to investigational medicinal product (IMP) were reported in the aripiprazole group compared with 29 (60.4%) in the placebo group. The most frequently reported TEAEs considered potentially casually related to IMP in either group were weight increased, insomnia, schizophrenia, and psychotic disorder. A total of 8 (8.2%) subjects in the aripiprazole group reported potentially causally related to IMP events (non-severe) of weight increased vs. 5 (10.4%) subjects in the placebo group.
The aripiprazole group reported fewer serious TEAEs (3 subjects [3.1%]) compared to the placebo group (6 subjects [12.5%]). The aripiprazole group also reported fewer severe TEAEs (2 subjects

[2.0%]) compared to the placebo group (5 subjects [10.4%]). The placebo group had 5 (10.4%) subjects with serious TEAEs of schizophrenia (3 moderate severity, 2 severe severity) and they represented impending relapse events compared to the aripiprazole group, who had 1 (1.0%) subject with a serious (mild severity) TEAE of schizophrenia. The aripiprazole group had 2 (2.0%) subjects with serious TEAEs of psychotic disorder (moderate severity) compared to the placebo group who had 1 (2.1%) subject with a serious TEAE of psychotic disorder (moderate severity).
No deaths or pregnancies were reported during the trial. The aripiprazole group had 20 (20.4%) subjects with TEAEs that led to the discontinuation of trial medication in the double-blind maintenance phase and the placebo group had 19 (39.6%) subjects. Schizophrenia was most frequently reported TEAE that led to discontinuation of trial medication (10 (10.2%) subjects in aripiprazole group and 13 (27.1%) subjects in placebo group). Patients with impending relapse events were required to discontinue the study and the relapses were captured as schizophrenia or psychotic disorder.
No adverse events of special interest (extrapyramidal symptoms (EPS), neuroleptic malignant syndrome (NMS), seizures, orthostasis, suicide, sedation/somnolence, glucose levels, lipid parameters, weight gain, prolactin levels, and hepatic functioning) occurred more frequently in the double-blind maintenance phase in the aripiprazole group compared to the placebo group. The most common adverse events of special interest reported was akathisia, which was reported by 3 subjects (6.3%) in the placebo group and 3 subjects (3.1%) in the aripiprazole group. No subjects experienced AEs relating to NMS, seizures, orthostasis, glucose levels, or prolactin.
No notable differences were seen between aripiprazole and placebo treatments in New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY AACENT) or Udvalg for Kliniske Undersøgelser (UKU) scales, the Columbia-Suicide Severity Rating Scale (C-SSRS) and there was no evidence of delay in sexual maturation associated with aripiprazole treatment, based on Tanner staging.
There was no mean change from baseline in EPS-rating scales (Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS) and the (Barnes Akathisia Rating Scale (BARS) in the double-blind maintenance phase. The only statistical difference was seen in the mean change from baseline in the AIMS, based on the OC dataset, at Week 16 ($p = 0.0365$) in the aripiprazole treatment group.
In the double-blind maintenance, there was no statistical difference between treatment groups in the mean change from baseline in Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) total score by week. Results from the mean by week in the P-QLES-Q overall score for the LOCF dataset showed subjects in the aripiprazole groups stayed about the same and placebo decreased (worsened). Results from the mean by week in the P-QLES-Q overall score for the OC dataset showed an increase (improvement) by Week 24 in the aripiprazole group and then a decrease by Week 52 to the baseline mean. The placebo group showed an increase from baseline in mean at Week 24 and 52 and then a decrease by last visit.

Laboratory Assessments, Vital Signs, ECG

No clinically meaningful changes from baseline were observed in serum chemistry, haematology, urinalysis or other laboratory test parameters in the double-blind maintenance phase, including serum prolactin concentrations. The frequencies of potentially clinically relevant laboratory values were comparable for aripiprazole and placebo treatment with the exception of prolactin (58 [59.2%] subjects in the aripiprazole group and 13 [27.1%] subjects in the placebo group). Despite the laboratory values reported, these subjects remained asymptomatic. There were very few TEAEs reported that were related to clinical laboratory test abnormalities in either treatment group. The aripiprazole group reported clinical laboratory test TEAEs of leukopenia and increased level of blood insulin in 2 (2.0%) subjects each.

No clinically meaningful changes from baseline were observed in vital sign parameters or ECG parameters in the double-blind maintenance phase. The incidence of potentially clinically relevant ECG measurements was similar for the aripiprazole and placebo treatment groups. ECG-related TEAEs were reported more frequently in the aripiprazole group than in the placebo group. One (2.1%) subject in the placebo group reported a TEAE of tachycardia. In the aripiprazole group 2 (2.0%) subjects reported a TEAE of tachycardia and 2 (2.0%) subjects reported a TEAE of arrhythmia.

Laboratory Measurements of Special Interest

Overall it is concluded that 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), serum glucose level and systolic and diastolic blood pressure.

A total of 24 (16.4%) subjects reported a potentially clinically relevant weight gain ≥7 % during the double-blind maintenance phase: 20 (20.4%) in the aripiprazole group and 4 (8.3%) in the placebo group. TEAEs related to weight increased were reported by 8 (8.2%) subjects in the aripiprazole group and 5 (10.4%) subjects in the placebo group. A total of 15 (10.3%) subjects (11 (11.2%) aripiprazole group and 4 (8.3%) placebo) reported a potentially clinically relevant increase ≥15 mmHg in standing diastolic blood pressure.

BENEFITS AND RISK CONCLUSIONS

The results of Trial 31-09-266 confirm that aripiprazole is efficacious in the maintenance treatment in adolescent patients aged 13 to 17 years with schizophrenia.

For the primary efficacy endpoint, aripiprazole was superior to placebo as measured by time to exacerbation of psychotic symptoms/impending relapse ($p = 0.0161$). Secondary efficacy endpoints also support the efficacy of aripiprazole compared to placebo. There was a statistically significant delay in time to exacerbation of psychotic symptoms / impending relapse for aripiprazole-treated subjects. The overall rate of exacerbation of psychotic symptoms/impending relapse was lower in the aripiprazole-treated subjects (19.39%) compared to placebo-treated subjects (37.50%) and greater proportion of subjects treated with placebo met at least one of the exacerbation of psychotic symptoms / impending relapse criteria compared to aripiprazole-treated subjects ($p = 0.0181$).

The difference in the percentage of aripiprazole-treated subjects who were responders at the last visit compared to placebo-treated subjects was not statistically significant ($p = 0.0962$). For evaluation of remission, 48 of 98 aripiprazole subjects and 19 of 48 placebo subjects met the 6 month threshold for the remission analysis. Of those, 21 of 48 aripiprazole subjects and 8 of 19 placebo subjects met the pre-set criteria for remission ($p = 0.9025$).

A statistically significant difference in the time to discontinuation prior to Day 378, for reasons other than sponsor terminated the trial, in the double-blind maintenance phase, was seen in the placebo subjects compared to aripiprazole subjects ($p = 0.0076$).

In general, symptom stability was maintained in the aripiprazole group, as measured by lack of change in the PANSS total, positive, negative, CGI-I and CGI-S scores, and worsened in placebo. However, the differences in the adjusted mean changes from baseline, based on the LOCF dataset, between aripiprazole- and placebo-treated subjects were not statistically significant. There were no consistent statistical findings in the other efficacy analyses.

The aripiprazole and placebo groups reported a similar percentage of TEAEs in the double-blind maintenance. The most frequently reported TEAEs in either treatment group were schizophrenia/psychotic disorder, insomnia, psychotic disorder, and weight increased. The aripiprazole group reported fewer serious TEAEs than the placebo group in the double-blind maintenance. No adverse events of special interest occurred with more frequency in aripiprazole-treated subjects as compared to placebo in the double-blind maintenance.

No clinically meaningful changes from baseline were observed in vital sign parameters or ECG parameters, in serum chemistry, haematology, urinalysis or other laboratory test parameters in the double-blind maintenance phase, including serum prolactin concentrations.
No possibly drug-induced liver events were reported. Weight and BMI changes were consistent with aripiprazole paediatric data for subjects aged 13 to 17 years. No notable differences were seen between aripiprazole and placebo treatments in NY-AACENT or UKU scales, and there was no delay in sexual maturation associated with aripiprazole treatment, based on Tanner staging.
As the follow-up, long-term, open-label safety trial of aripiprazole in adolescent patients with schizophrenia (Protocol 31-09-267) is ongoing and delivering more safety data for this population at the present time the MAH is not proposing a change to the aripiprazole SmPC.

Assessment

MAH has presented the final results of the multicentre, randomised, double-blind, placebo-controlled study to evaluate the long-term efficacy, safety, and tolerability of aripiprazole as maintenance treatment in adolescent patients aged 13 to 17 years with schizophrenia. This was a Paediatric Investigation Plan (EMEA-000235-PIP02-10-M02) for the treatment of schizophrenia in patients 13 to 17 years of age in order to demonstrate the maintenance of effects.

Analysis of data do not raise particular concerns in efficacy beyond 12 weeks in the presented indication. The fact that the study was interrupted when most (ca. 90%) patients had not reached endpoint preclude the chance to obtain more sound data regarding efficacy and safety. The stopping rules for the study were reached very early (some patients remained in the study in maintenance phase for only 6 days), and apparently this was not expected nor foreseen, as this low threshold for study discontinuation (after the 37th patient suffering impending relapse event) was not challenged by at the time of advice. Nevertheless presented efficacy data do not jeopardise any of the EU approved indications.

For safety, there were relevant adverse events occurring in paediatric population, both in frequency and in severity, as compared to the adult population, namely concerning weight gain but were not different from what has been seen in the pediatric population in other indications, and are in line with the adverse event profile observed in the main studies which led to approval of the paediatric indications.

The drop out rate due to lack of efficacy and / or adverse events was lower than what has been described, but this was artificially kept low due to the early termination of the study. This aspect will be better identified in the ongoing open label study.

Adverse event values are within the range of both aripiprazole in other indications and age ranges and of other antipsychotics in schizophrenia.

MAH has declined to advance a change to PI, proposing to only suggest modifications to SmPC after the results from the open label extension become available. This proposal is acceptable, since relevant uncertainties remain unanswered.

II. RAPPORTEUR'S OVERALL CONCLUSION AND FURTHER ACTION IF REQUIRED

This long-term, multicentre, randomised, double-blind, placebo-controlled Study was to evaluate the efficacy, safety, and tolerability of Aripiprazole (OPC-14597) as Maintenance Treatment in Adolescent Patients with Schizophrenia.

The study involved a population (13 and 14 YO) not approved in Europe. Efficacy data analysis was restricted to the primary and key secondary endpoints. Early termination prevented all the other endpoints to be statistically or clinically significant. So far no new safety issues have arisen in comparison with the AE profile of EU approved population.

As a PIP request to ascertain persistence of efficacy, an update to SPC should follow, to insert relevant data from this study in PI. However, since the double blind study was early terminated and relevant and robust data was not available, MAH does not propose to change the SPC and proposes to wait for the analysis of the long-term open label extension. This proposal is endorsed, meaning that a follow up to this PAC is expected, to present long term safety and tolerability data to CHMP.