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Human Medicines Development and Evaluation

Abilify

International non-proprietary name: Aripiprazole

Procedure no.: EMA/H/C/000471/P46 - 066

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

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Introduction

On 11 March 2013 the MAH submitted a completed paediatric study for Abilify, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Scientific discussion

Information on the development program

The MAH stated that study "31-05-243: An open-label, rollover study for subjects completing Abilify (Aripiprazole) Clinical Study 31-03-241" is part of a clinical development program for the paediatric treatment of schizophrenia. The variation application consisting of the full relevant data package is expected to be submitted by 2016. A line listing of all the concerned studies is annexed.

Conduct of the presented trial is not a requirement of the Paediatric Investigation Plan for aripiprazole (EMEA-000235-PIP02-10-M02) and the MAH is not proposing a change to the aripiprazole Summary of Product Characteristics (SmPC) based upon the study results.

Aripiprazole is an atypical antipsychotic that is approved via the centralized 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).

Aripiprazole is also approved in a variety of indications in other countries.

Information on the pharmaceutical formulation used in the study(ies)

The study used the US commercially available tablet formulation of aripiprazole (2, 5, 10, and 15 mg).

Clinical aspects

1. Introduction

The MAH submitted a final report for:

• Trial 31-05-243: An open-label, multinational, non-comparative rollover trial designed to continue to provide aripiprazole on a compassionate use basis to adolescents and adults with schizophrenia who complete Trial 31-03-241;

2. Clinical study

Description

Trial 31-05-243 was an open-label rollover study designed to provide continued treatment with aripiprazole at doses ranging from 5 to 30 mg on a compassionate use basis to adolescents (13 to 17 years of age) or young adults (adolescents who reached 18 years during the open-label parent trial (Trial 31-03-241) or previous double-blind trial (Trial 31-03-239) with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV).

Methods

• Objective

The primary objective of this trial was to continue to provide aripiprazole therapy (5 mg, 10 mg, and/or 15 mg tablets) to subjects with schizophrenia who completed the Otsuka-sponsored open-label safety and tolerability Trial 31-03-241.

• Study design

Trial 31-05-243 was an open-label, multicenter, non-comparative rollover trial designed to continue to provide aripiprazole on a compassionate use basis in doses ranging from 5 to 30 mg to adolescent (13 to 17 years of age) and adult (adolescents who reach 18 years during the open-label parent trial [Trial 31-03-241] or previous double-blind trial [Trial 31-03-239]) male and female subjects with a diagnosis of schizophrenia according to DSM-IV. Subjects were required to complete Trial 31-03-241 in order to be eligible for the current rollover trial. Trial 31-03-241 was a multicenter, open-label trial that provided up to 6 months of aripiprazole for subjects completing Trial 31-03-239, a randomized, comparative trial in which adolescents with a DSM-IV diagnosis of schizophrenia received double-blind treatment (aripiprazole or placebo) for 6 weeks. The DSM-IV diagnosis of schizophrenia was as confirmed by a Kiddie-Sads-Present and Lifetime Version interview initially conducted for eligibility to enroll in Trial 31-03-239 (no additional confirmatory diagnostic evaluations were performed for Trial 31-03-241 or the current trial).

This trial was intended for countries where aripiprazole was not yet commercially available and/or reimbursed. This trial was conducted in Argentina, Bulgaria, Croatia, India, Russian Federation, Serbia and Montenegro, South Africa, and Ukraine at 35 trial centers (one additional center was initiated but did not enroll subjects).

Informed consent from the responsible adult (or potentially from the subject if 18 years of age) and assent of the child (if applicable) were obtained and documented with the opportunity to have all questions answered prior to completion of any trial-related assessments. Participation in the rollover trial was considered on an individual basis if enrollment criteria were met. Subjects retained the same identification number throughout the open-label and double-blind trials. The End of Treatment (EOT) evaluations conducted at the last visit of Trial 31-03-241 served as the baseline evaluations for Trial 31-05-243. Subjects attended 4 trial visits during the first year of treatment (Months 3, 6, 9, and 12), 3 visits during the second year of treatment (Months 15, 18, and 24), and visits every 6 months thereafter (Months 30, 36, 42, 48, 54, 60, 66, and 72/early termination [ET]). Subjects were

contacted by phone at monthly intervals between scheduled visits to assess the occurrence of adverse events (AEs). Follow-up phone calls were made 14 ± 2 days after the last trial visit to assess the status of ongoing AEs and to record the occurrence of new serious AEs (SAEs). Each subject received daily aripiprazole at a dose between 5 and 30 mg (maximum allowed dose), as previously established in the 31-03-241 safety and tolerability trial; however, modifications to the daily dose could be made at the investigator's discretion, if clinically warranted.

Subjects who enrolled into this trial were permitted to receive psychotropic medications with the exception of other antipsychotic agents and could continue any concomitant medications permitted during Trial 31-03-241. Safety data were derived from AE reporting, physical examinations, clinical laboratory tests, urine pregnancy tests (all female subjects), electrocardiograms (ECG), and measurements of vital signs (including body weight), body mass index (BMI), and waist circumference. A Clinical Global Impression - Severity (CGI-S) scale was completed to assess the continuation of therapeutic benefit from aripiprazole treatment as determined by the investigator. The Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) was completed to assess the subject's perception of treatment benefit and was administered in translated languages, when available. The Columbia-Suicide Severity Rating Scale (C-SSRS) was administered to assess the risk of suicide events and to classify reported suicide events (per Amendment 003 of trial protocol, approved 28 Oct 2009).

Aripiprazole treatment and trial visits continued until there was a clinical or administrative reason for discontinuation. Clinical reasons included, but were not limited to: voluntary withdrawal, treatment intolerance, lost to follow-up, and lack of continued benefit per the investigator. Administrative reasons included, but were not limited to: commercial availability of and/or reimbursement for aripiprazole, termination of aripiprazole development by the sponsor, or the trial reached the planned trial end date of 31 Dec 2012. Once aripiprazole became commercially available and/or reimbursed in the country where a subject was participating in the trial, treatment with aripiprazole in Trial 31-05-243 was to be discontinued within a reasonable period of time (approximately 1 to 3 months) and the subject was to be transitioned to commercially available aripiprazole (Abilify) or another treatment option as deemed appropriate by the investigator. For purposes of this trial, subjects who completed the last scheduled visit during the treatment period, ie, the Month 72 visit (or the last scheduled visit within 6 months before 31 December 2012), were defined as trial completers.

- Study population /Sample size

Subjects were directly enrolled into the current open-label, non-comparative rollover trial from the previous open-label parent Trial 31-03-241; therefore, no predetermined sample size was calculated. A maximum of 200 subjects were expected to be enrolled. The number of male and female subjects enrolled in the trial was balanced (43 males, 42 females). The mean age at trial entry (defined as the last scheduled visit in the previous Trial 31-03-241) was 16.3 years (range 13 to 18 years). The majority of subjects (66/85, 77.7%) were between 13 to 17 years of age; the remaining subjects (19/85, 22.4%) were 18 years of age at trial entry. Mean BMI was relatively similar between males and female subjects (21.9 and 23.2 kg/m2, respectively). The majority of subjects were Caucasian (49/85, 57.7%); the remaining subjects were Asian (24/85, 28.2%), 'Other' (11/85, 12.9%), or American Indian or Alaska Native (1/85, 1.2%). All 85 enrolled subjects were included in the safety analysis. A total of 84/85 subjects (98.8%) were included in the analysis of efficacy and quality of life outcome measures.

- Treatments

Aripiprazole was manufactured by either Otsuka Pharmaceutical Co., Ltd. (Japan) or Bristol-Myers Squibb Co. (Mayaguez, Puerto Rico) and provided through commercial supply as oral tablets in

strengths of 5 mg, 10 mg, and 15 mg. The lot numbers used in Trial 31-05-243 were as follows:

Dose of Aripiprazole	Lot numbers
5 mg	5F4207A, 5G4212A, 6F16559, 8F39832A, 9K57701B
10 mg	5E4218A, 5G4204A, 6F20935, 8F35169B, 9K47475B
15 mg	5F4211A, 5K02919, 6G11436, 8B33344A, 9K57897D

All trial medication was provided in bottles containing 30 tablets in each bottle and dispensed as a 3-month supply.

- Outcomes/endpoints

Primary Outcome Measures

The following primary safety variables were summarized:

- Frequency and severity of treatment-emergent adverse events (TEAEs),
- Frequency and severity of treatment-emergent SAEs (including AEs related to clinical laboratory abnormalities),
- Rates of discontinuation from the trial due to TEAEs.

Secondary Outcome Measures

Safety variables

- Reported AEs (in addition to the primary safety variables) including summarization of TEAEs by causality, severity, and gender, as well as the incidence of deaths
- Clinical laboratory tests (including routine serum chemistry, hematology, and urinalysis analyses as well as creatine phosphokinase [CPK]; fasting insulin, serum glucose, triglycerides, high-density lipoprotein cholesterol [HDL-C]; glycosylated hemoglobin [HbA1c]; and serum prolactin)
- Vital sign parameters (supine and standing blood pressure and pulse rate, body temperature, and respiration rate) and physical examination (including height and weight for calculation of BMI and measurement of waist circumference)
- ECGs
- Percentage of subjects showing significant weight gain or loss (weight gain or loss of 7% relative to baseline)
- C-SSRS

For the purpose of this report, fasting serum triglycerides, HDL-C, and glucose levels; BMI and waist circumference; and supine and standing systolic and diastolic blood pressure were also evaluated as part of the metabolic syndrome evaluation. Adverse events of special interest were also summarized.

Efficacy variables

The following efficacy variable was evaluated by visit:

- Mean change from baseline in CGI-S score

Other variables

- The following quality of life outcome variables were evaluated by visit:

- Mean change from baseline in P-QLES-Q Total Score
- Mean change from baseline in P-QLES-Q Overall Score

- Statistical Methods

Safety Methods: Safety analyses were conducted on the safety dataset, defined as all enrolled subjects who received at least one dose of open-label trial medication. Safety data were summarized using descriptive statistics, as appropriate. Treatment-emergent adverse events for this analysis were defined as any AE with onset after the first dose of open-label aripiprazole in Trial 31-05-243 or any event which continued from baseline and became serious, was classified as related to trial drug, or resulted in death, discontinuation, interruption or reduction of dose. The incidences of TEAEs were summarized for all TEAEs, TEAEs by severity, potentially drug-related TEAEs, treatment-emergent SAEs, and discontinuations due to TEAEs. Adverse events were examined by gender as well as overall incidence. Descriptive statistics were used to summarize original values, change from baseline at each scheduled visit, and change from baseline to the last visit for the continuous safety variables. Incidences of metabolic syndrome abnormalities were summarized by visit, overall and by gender. Potentially clinically significant changes in laboratory parameters, ECG findings, vital signs, weight, and metabolic syndrome abnormalities were identified using prospectively-defined criteria. The age of subjects on the date of the trial visit was used for age-dependent criteria. QT intervals were corrected for heart rate (QTc) based on several formulas, including Bazett's formula (QTcB). Data collected on the C-SSRS were listed for ongoing subjects as Amendment 003 to the protocol was implemented.

Efficacy Methods: Efficacy (CGI-S score) and other outcome variables (P-QLES-Q Total and Overall scores) were summarized as change from baseline using descriptive statistics. Subjects with missing baseline or post-baseline efficacy and other outcome measurements were not included in the descriptive statistics for those variables or in the descriptive statistics for change from baseline to postbaseline. No missing data were imputed for analyses by visit; an observed case (OC) analysis was considered more appropriate than data imputation. However, data were summarized for the last available visit as an additional evaluation of these variables. No inferential statistical analyses were performed for any efficacy, safety, or other outcome variables.

Results

- Recruitment/ Number analysed

No predetermined sample size was calculated. A total of 85 subjects who completed Trial 31-03-241 were actually enrolled. The majority of subjects remained in the trial for at least 24 months: 78.8% completed at least 12 months and 51.8% completed at least 24 months of treatment. Fourteen (of 85) enrolled subjects (16.5%) completed at least 66 months (5.5 years) of treatment with open-label aripiprazole in the trial; of these, 13 (of 85) subjects (15.3%) completed the trial. Overall, 72/85 subjects (84.7%) were prematurely discontinued from the trial. The two most common reasons for discontinuation were the subject having met the withdrawal criteria (22/85 subjects, 25.9%) and the subject withdrew consent (19/85 subjects, 22.4%). The incidence of subjects who discontinued from the trial due to lack of efficacy was low (3/85 subjects, 3.5%). Seven (of 85) subjects (8.2%)

- Baseline data

Baseline characteristics were those reported at End Of Study 31-03-241 visit, and were not detailed in the report.

- Efficacy results

No primary efficacy variable was defined for this trial.

Secondary Efficacy:

Severity of illness was rated at all scheduled trial visits. For CGI-S, a lesser mean score indicates less severity of illness. Evaluation of efficacy based on mean change from baseline in CGI-S score indicated that efficacy was generally maintained in subjects who had previously received flexible daily doses of open-label aripiprazole (5 to 30 mg) in Trial 31-03-241 and continued treatment with open-label aripiprazole in the current long-term safety and tolerability trial. Mean scores for CGI-S generally decreased from baseline at each successive post-baseline visit up to the Month 72 scheduled visit (mean change from baseline ranged from -0.15 at Month 3 [n = 81] to a maximum change of -0.64 at Month 66 [n = 14]). Overall, the mean change from baseline (mean = 2.37) to the last visit (mean = 2.11) for CGI-S was -0.26 [Standard Deviation (SD)=1.07, n = 84].

Other Quality of Life Outcomes:

The P-QLES-Q was completed by the subject twice a year in translated languages to assess the subject's quality of life (higher numeric ratings indicate greater satisfaction). The rating on the P-QLES-Q Total Score (sum of Items 1 to 14) indicated that on average the subjects' quality of life, enjoyment, and satisfaction were generally maintained from baseline (51.51) to the last visit (53.80) with continued long-term treatment of open-label aripiprazole (mean change from baseline was 2.29 [n = 79]). Mean changes from baseline were minimal at each scheduled visit (range: maximum increase of 2.49 at Month 18 [n = 55] to a maximum decrease of -4.43 at Month 66 [n = 14]). The rating on the P-QLES-Q Overall Score (Item 15) indicated that, on average, the subjects' overall quality of life was maintained as fair to good from baseline (3.90) to the last visit (3.94) (mean change from baseline was 0.04 [n = 82]). Mean changes from baseline on the PQLES- Q Overall Score were also generally minimal (range: 0.21 at Month 18 [n = 57] to -0.57 at Month 66 [n = 14]).

•Safety results

Safety Results:

Extent of Exposure:

All 85 enrolled subjects received at least one dose of trial medication and were included in the safety analysis set. The average daily dose of open-label aripiprazole during the trial was 17.1 mg (ranging from 5 to 30 mg). The percentage of subjects exposed to trial medication for the longest possible duration (up to 67 months [2030 days]) was 15.3% (13/85 subjects), at an average daily dose of 18.3 mg. Cumulative exposure to aripiprazole over the duration of the trial was 205 subject years. This exposure is in addition to the 26 to 32 weeks of exposure to aripiprazole received in the previous trials (Trial 31-03-239 and Trial 31-03-241).

Adverse Events:

An overview of AEs is presented in the following table:

Summary of Adverse Events			
Number of:	**Aripiprazole**		
	Males	**Females**	**Total**
Subjects treated,[a] N	43	42	85
Subject days of drug exposure[b]	34943	39836	74779
Subject years of drug exposure	95.7	109.1	204.7
Subjects with AEs, n (%)	31 (72.1)	30 (71.4)	61 (71.8)
AEs, N	97	164	261
Subjects with TEAEs, n (%)	31 (72.1)	30 (71.4)	61 (71.8)
TEAEs, N	89	134	223
Subjects with SAEs, n (%)	5 (11.6)	6 (14.3)	11 (12.9)
Subjects with severe TEAEs, n (%)	1 (2.3)	5 (11.9)	6 (7.1)
Subjects who discontinued trial medication due to TEAEs, n (%)	2 (4.7)	5 (11.9)	7 (8.2)

AEs = adverse events; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

a Safety population on which all percentages are based.

b Calculated as the sum of drug end date minus drug start date + 1 for all subjects.

Overall, 61/85 subjects (71.8%) experienced a total of 223 TEAEs during the trial. The percentage of subjects who experienced at least one TEAE was relatively balanced between genders (71.4% for females and 72.1% for males). The majority of all TEAEs were either mild or moderate; 6/85 subjects (7.1%) experienced at least one severe TEAE.

The most frequently reported TEAEs (incidence ≥ 5% in the total population) by decreasing frequency were headache (13/85 subjects, 15.3%), influenza and increased weight (each 9/85 subjects, 10.6%), pyrexia (8/95 subjects, 9.4%), vomiting and pain (each 7/85 subjects, 8.2%), nasopharyngitis (6/85 subjects, 7.1%), and nausea, decreased appetite, somnolence, anxiety, and cough (each 5/85 subjects, 5.9%).

The most frequently reported potentially drug-related TEAEs (incidence of ≥3% of subjects overall) were increased weight (8/85 subjects, 9.4%), somnolence (4/85 subjects, 4.7%), and nausea, decreased appetite, headache, and tremor (each 3/85 subjects, 3.5%). One death, attributed to a serious event of bacterial pneumonia, was reported in this trial. The fatal event was considered severe and unrelated to trial medication. The subject had received 1546 days of trial medication (30 mg/day aripiprazole) at onset of the event. Eleven (of 85) subjects (12.9%) experienced at least one treatment-emergent SAE during the trial. Treatment-emergent SAEs reported in more than one subject included suicide attempt (3/85 subjects, 3.5%) and schizophrenia (2/85 subjects, 2.4%). The following SAEs were reported by 1 subject each: bacterial pneumonia, ligament rupture, psychomotor hyperactivity, aggression, impulsive behaviour, psychotic disorder, and social stay hospitalisation. Six of the 11 subjects experienced a treatment-emergent SAE that led to discontinuation of trial medication.

Seven (of 85) subjects (8.2%) discontinued trial medication due to at least one TEAE. Suicide attempt was the only TEAE that led to discontinuation in more than one subject (2/85 subjects, 2.4%). All TEAEs that led to discontinuation of trial medication were categorized by the investigator as either moderate (schizophrenia and 1 event of suicide attempt) or severe (bacterial pneumonia, aggression, psychotic disorder, hypertension, and 1 event of suicide attempt).

Adverse events of special interest were summarized for the trial.

- EPS
  Ten (of 85) subjects (11.8%) experienced at least one treatment-emergent extrapyramidal

symptom (EPS)-related AE during the trial. Tremor and muscle rigidity were the only EPS-related AEs reported in more than one subject. One EPS-related AE was considered serious (psychomotor activity). There were no TEAEs of either tardive dyskinesia or neuroleptic malignant syndrome, and there were no seizures, hyperglycemia/diabetes, or orthostatic hypotension-related TEAEs reported during the trial.

- Suicidality
  Four subjects experienced a suicide-related TEAE, including 3 subjects who reported a suicide attempt and 1 subject who experienced intentional self-injury during the trial. All 3 events of suicide attempt were considered serious; 2 of these 3 events led to discontinuation of trial medication (none were considered related to trial medication). The fourth event (intentional self-injury) was reported as a non-serious TEAE (considered mild and not likely related to trial medication).

- Other
  Other TEAEs of special interest reported by at least one subject included increased weight (9/85 subjects, 10.6%), decreased appetite (5/85 subjects, 5.9%), increased blood CPK (1/85 subjects, 1.2%), and abnormal behaviour (1/85 subjects, 1.2%).

Pregnancy:

No pregnancies were reported in female subjects enrolled in the trial. One pregnancy was reported for the female partner of male subject (the 6-month follow up call indicated that the baby was healthy with no known growth deviations).

Clinical Laboratory Results:

None of the mean changes from baseline for any of the serum chemistry laboratory, hematology, or urinalysis tests were considered to be clinically significant.

Potentially clinically significant increases in total bilirubin (defined as ≥ 2.0 mg/dL for ages 13 to 17 years and 18 years and older) were observed in 7/79 subjects (8.9%) and potentially clinically significant increases in total CPK (defined as > 500 U/L for ages 13 to 17 years; ≥ 3.0 * ULN for 18 years and older) were observed in 6/79 subjects (7.6%) during the trial. Serum chemistry laboratory abnormalities that were reported as TEAEs included increased blood bilirubin (1 subject), increased blood CPK (1 subject), hyperkalaemia (1 subject), and hypercholesterolaemia, hyperlipidaemia, and hypertriglyceridaemia (1 subject). Potentially clinically significant changes in eosinophils and hematocrit (each 5/79 subjects, 6.3%) and hemoglobin (3/79 subjects, 3.8%) were also observed. No clinically relevant changes in hematology parameters were observed during long-term treatment with aripiprazole. Overall, mean changes from baseline in serum prolactin were relatively minimal and the range of mean change was similar between males and females. Three subjects (2 male and 1 female) had a single potentially clinically significant elevated prolactin value (defined as > 1 X ULN) at some point during the trial. The overall incidence of low prolactin levels (where low serum prolactin levels are defined as < 3 ng/mL for females and < 2 ng/mL for males) was 35.4% (28/79 subjects). The incidence of low prolactin levels was greater in males (18/40 subjects, 45.0%) compared to females (10/39 subjects, 25.6%).

Vital Sign Parameters:

None of the mean changes from baseline for any of the vital sign parameters were considered to be clinically significant. The most common potentially clinically significant vital sign abnormalities (incidence ≥ 5% of all subjects) included increases in standing systolic blood pressure and supine and standing diastolic blood pressure (each observed in 5/84 subjects, 6.0%). No clinically significant orthostatic changes in blood pressure were observed. One subject experienced a clinically significant

increase in blood pressure that was reported as a severe TEAE of hypertension (onset on Day 1095) that led to discontinuation from trial medication.

Electrocardiogram Evaluation:

No clinically meaningful changes in any ECG parameters were observed. Nine (of 82) subjects (11.0%) experienced a potentially clinically significant increase in QTcB during the trial; 3 of these 9 subjects also met the criteria for potentially clinically significant increase in QTcF. No QTc prolongations exceeded 500 msec during the trial and none were reported as TEAEs.

Other Safety Variables

Although small mean increases from baseline in waist circumference and BMI were observed with each postbaseline visit, no clinically meaningful changes from baseline were observed in any of the metabolic syndrome evaluation parameters (for males or females) during the trial. Overall, no clinically meaningful trends were observed in the incidence of metabolic syndrome abnormalities between baseline and the last visit. Overall, 37/82 subjects (45.1%) had a potentially clinically significant increase in weight (≥ 7% increase compared to baseline) and 4/82 subjects (4.9%) had a potentially clinically significant decrease in weight (≥ 7% decrease compared to baseline) at the last visit of the trial. Nine (of 85) subjects (10.6%) experienced weight gain that was reported as a TEAE during the trial. Two (of 85) subjects (2.4%) experienced weight loss that was reported as a TEAE. None of the TEAEs related to change in weight led to discontinuation from the trial. Overall, mean changes from baseline to the last visit were within 0.5 SD of the general population for weight z-scores and within 1.0 SD of the general population for BMI z-scores; mean changes from baseline at each trial visit for both weight and BMI z-scores were negligible. One subject responded “yes” to an actual attempt (non-suicidal self-injurious behaviour) on the suicidal behaviour category of C-SSRS at the Month 66 visit. The subject’s behaviour was reported as a non serious TEAE (preferred term: intentional self-injury) on Day 1400. The event was considered mild and not likely related to trial medication.

Conclusions:

- Long-term administration of open-label aripiprazole (up to 67 months [2030 days]) was well-tolerated at flexible daily doses of 5 to 30 mg in adolescent and adult subjects with schizophrenia. The average daily dose of open-label aripiprazole administered during the trial was 17.1 mg. Fourteen (of 85) enrolled subjects (16.5%) completed at least 66 months (5.5 years) of treatment with open-label aripiprazole. The incidence of subjects who discontinued from the trial due to lack of efficacy was low (3.5%) and 8.2% of subjects discontinued from the trial due to AEs.
- Efficacy was maintained in adolescent or adult subjects with schizophrenia who completed the previous open-label safety and tolerability Trial 31-03-241 and continued to receive long-term treatment with flexible daily doses of 5 to 30 mg open-label aripiprazole in the current trial, as indicated by minimal changes in CGI-S score (range: .0.15 at Month 3 to a maximum change of 0.64 at Month 66). Overall, the mean change from baseline to the last visit was 0.26.
- Quality of life was evaluated by the P-QLES-Q during long-term treatment of open-label aripiprazole. Quality of life, enjoyment, and satisfaction were generally maintained during long-term treatment as indicated by minimal change on P-QLES-Q Total and Overall Scores for the duration of the trial (mean changes from baseline to last visit were 2.29 and 0.04, respectively).
- Long-term administration of open-label aripiprazole was generally safe and no new AEs of concern were identified. Overall, 71.8% of all subjects experienced at least one TEAE, with the majority of TEAEs reported as mild or moderate. The most frequently reported TEAEs

(incidence ≥5% of all subjects) were headache (15.3%), influenza and increased weight (each 10.6%), pyrexia (9.4%), vomiting and pain (each 8.2%), nasopharyngitis (7.1%), and nausea, decreased appetite, somnolence, anxiety, and cough (each 5.9%). Eleven (of 85) subjects (12.9%) experienced treatment-emergent SAEs during the trial, including one death. The death was attributed to bacterial pneumonia and was unrelated to trial medication. Treatment-emergent SAEs reported by more than one subject included suicide attempt (3 subjects) and schizophrenia (reported term: worsening of schizophrenia; 2 subjects). Seven (of 85) subjects (8.2%) discontinued trial medication due to a TEAE; all but one of the TEAEs that led to discontinuation (hypertension) was considered serious.

- Ten (of 85) subjects (11.8%) experienced treatment-emergent EPS-related AEs during long-term administration of aripiprazole to adolescents and adults with schizophrenia. Tremor and muscle rigidity were the only EPS-related AEs reported in more than one subject. All EPS-related AEs were mild or moderate in severity, with exception of 1 severe event of psychomotor hyperactivity (also considered serious).
- Four (of 85) subjects experienced a suicide-related TEAE, including events of suicide attempt (3 subjects) and intentional self-injury (1 subject). All 3 events of suicide attempt were considered serious, and 2 of these 3 led to discontinuation of trial medication. One subject recorded a positive response on the C-SSRS (reported as the TEAE of intentional self-injury). There were no TEAEs related to seizure or hyperglycemia/diabetes and no individual TEAEs of tardive dyskinesia, neuroleptic malignant syndrome, or orthostatic hypotension were reported.
- There were no clinically meaningful changes from baseline in serum chemistry or hematology clinical laboratory parameters during the trial. Potentially clinically significant changes in serum chemistry were limited to increases in total bilirubin (8.9%) and increases in CPK (7.6%).
- Mean changes from baseline in serum prolactin were relatively minimal and relatively similar between males and females. Three (of 79) subjects (3.8%) experienced a potentially clinically significant increase in prolactin; no TEAEs related to changes in prolactin were reported. The overall incidence of low prolactin levels (defined as < 3 ng/mL for females and < 2 ng/mL for males) was 35.4% (28/79 subjects). The incidence was greater in males (18/40, 45.0%) compared to females (10/39, 25.6%). The clinical relevance of these findings is unknown in the paediatric population.
- The incidence of potentially clinically significant vital sign abnormalities was low (≤5 subjects per parameter). No clinically significant orthostatic changes in blood pressure were observed. One subject experienced a severe TEAE of hypertension that led to discontinuation from trial medication; the event was considered not related to trial medication.
- No clinically meaningful changes in QTc intervals or other ECG parameters were observed during long-term treatment with aripiprazole. Nine (of 82) subjects (11.0%) experienced a potentially clinically significant increase in QTcB during the trial. No clinically meaningful trends were observed in the incidence of metabolic syndrome abnormalities between baseline and the last visit.
- Overall, 37/82 subjects (45.1%) had a potentially clinically significant increase in weight (≥7% increase compared to baseline) and 4/82 subjects (4.9%) had a potentially clinically significant decrease in weight (≥7% decrease compared to baseline) at the last visit of the trial. Mean changes from baseline to the last visit for weight and BMI z-scores were within 0.5 and 1.0 SD of the general population, respectively, and changes from baseline were negligible.

1. Discussion on clinical aspects

Several aspects must be discussed. The study took place outside western Europe, and only Bulgaria, Croatia, Russian Federation, Serbia and Montenegro and Ukraine were representatives of the European population. In some countries, the moment Abilify was marketed in that country, patients were withdrawn from the study – leading to early termination due to sponsor decision, and loss of follow up data. It is also known that in most of these countries the availability of other antipsychotics and other CNS agents like antidepressants and anxiolytics is limited, seldom mimicking European reality.

There were 49 Caucasian subjects among the 85 enrolled patients, which have been responding to Abilify and tolerating in the previous trial. No table was provided listing patients by age range, and withdrawals by age range. Since the study lasted up to 5.5 years, and that all patients at 18 years reached withdrawal criteria, the patients that completed the trial must have been 13 years or younger at inclusion. It is understood that this study was produced to reflect the US indication in schizophrenia. However, since the indication for schizophrenia in adolescents in Europe starts at 15 years, data should also be analyzed taking this aspect into consideration.

Secondary efficacy reflected the population that was enrolled in this study, which was composed of responders that were tolerating Abilify for the past months. Since several of the patients were withdrawn, and data are therefore missing, no further conclusions may be drawn.

Safety evaluation has evidenced some less expected results. Although EPS data did not divert from what is already known in this population, weight increase in around 10% of patients, was more than expected taking into consideration previous data in adolescents with schizophrenia. Waist circumference and BMI also increased during the trial, and overall 45% of the patients had a "potentially clinically significant" increase in weight (≥ 7% increase compared to baseline), while only 5% had a "potentially clinically significant" decrease in weight as compared to baseline.

Pain was also highly reported, with more than 8% of the population experiencing pain.This aspect should be followed, and consideration to include it in SmPC should be given.

Around 13% of adolescents had a Treatment Emergent SAE, 3.5% of these serious AEs were suicide attempts.

Other AEs were within the expected frequencies. Low serum prolactin was 25.6% in female and 45% in male adolescents, but this has been reported previously and its clinical importance is still unknown. Potentially clinically significant increases in total CPK (defined as > 500 U/L for ages 13 to 17 years; ≥ 3.0 * ULN for 18 years and older) occurred in 7.6% of patients, but in only one was reported as AE. Since these events were rare and with similar frequencies as pyrexia, this may be interpreted as a possibly related, particularly associated to viral infections, which are frequent in this age range.

Rapporteur's overall conclusion and recommendation

The data presented for the long term study in children and adolescents with schizophrenia do not reveal previously unknown events or weaning of efficacy in this aripiprazole responder population. However, the frequency of some events should be further discussed and detailed in the EU relevant age group (15-18 years), such as weight gain and suicidality. This discussion should also consider the need to update RMP for these aspects.

As for previous studies, the frequency of low prolactinaemia should be appended to section 4.8 of SmPC, such as:
"In the paediatric (13-17 years) schizophrenia population with aripiprazole exposure of 5 to 30 mg up

to 72 months, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 25.6% and 45.0%%, respectively."

Recommendation

☐ **Fulfilled**

No regulatory action required

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide a table listing separated by age range at baseline 12-14 years and 15-18 years, detailing withdrawals within each group. MAH should also further discuss weight gain and suicidality according to the EU relevant age range and their progression with treatment duration.

Additional clarifications requested

Based on the data submitted, the MAH should provide a table listing separated by age range at baseline 12-14 years and 15-18 years, detailing withdrawals within each group. MAH should also further discuss weight gain and suicidality according to the EU relevant age range and their progression with treatment duration.

The timetable as proposed by the Rapporteur is as follows:

a 30 day response timetable without clock stop will apply.

Rapporteur's assessment of MAH responses to RSI

Question 1:

Based on the data submitted, the MAH should provide a table listing separated by age range at baseline 12-14 years and 15-18 years, detailing withdrawals within each group.

RESPONSE:

Study 31-05-243: An open-label, multinational, non-comparative rollover trial designed to as a continuation to provide aripiprazole on a compassionate use basis to adolescents and adults with schizophrenia and bipolar I disorder only for patients who complete Study 31-03-241 and 31-03-239. Patients rolled-over to the study in 2006-2007 in 8 countries where aripiprazole was not marketed and/or reimbursed at the time of roll-over (Argentina, Bulgaria, Croatia, India, Russian Federation, Serbia and Montenegro, South Africa, and Ukraine). The study was designed to provide medication access to patients who participated in one of the parent-studies trial 31-03-241 or 31-03-239 and seemed to benefit from the treatment. The study didn't have a definite endpoint in terms of a set duration of exposure, however, the longest exposure was 72 months based on the commercial availability of aripiprazole in a particular country. Patients in each country were discontinued as commercial supply became available in that country. Over time a number of countries (Argentina, Russia, South Africa, Bulgaria) got discontinued all of their remaining patients due to the availability of Aripiprazole locally while some patients in other countries continued the study due to the lack of medication access until it reached the planned trial definite end date in 2012. Noteworthy is that most of the 31-05-243 patients were aged 13-17 years old at the time of roll-over, however, 19 patients

reached 18 years of age during the parent study (31-03-241 or 31-03-239) and remained eligible for and rolled over into the 31-05-243 study. The exposure of patients on study 31-05-243 varied from <1 months to 72 months therefore the reviewer needs to take into consideration that 46% of the patients became adults (19-23 years old) by the time of study discontinuation (see Table 3).

As noted before, patients got discontinued in a participating country once aripiprazole became locally commercially available therefore this needs to be taken to account during the evaluation of withdrawals. Overall, 72/85 subjects (84.7%) discontinued from the trial. The 2 most common reasons for discontinuation were the subject having met the withdrawal criteria (22/85 subjects, 25.9%) and the subject withdrawing consent (19/85 subjects, 22.4%). A manual review of the by-subject listing of reasons for discontinuation indicated that 20 of the 72 subjects [27.8%] who discontinued overall were discontinued due to aripiprazole having become commercially available in the country where the subject was participating during the course of the trial. The incidence of subjects who discontinued from the trial due to lack of efficacy was low (3/85 subjects, 3.5%). Seven (of 85) subjects (8.2%) discontinued from the trial due to AEs.

The 12-14 years old group consist of 9 patients aged 13-14 years at baseline (no patient was below 13) and 76 patients were 15-18 years old at baseline when entering study 31-05-243.

Table 1 Discontinuation table of 12-14 years old patients detailing withdrawals over 72 months of exposure:

DISCONTINUATION OF 12-14 YEARS OLD (AGE AT BASELINE) GROUP BY RESASON (N=9)		
Reason of DC	**Number of event**	**% Event DC**
Subject met withdrawal criteria	3	33%
Subject Withdrew consent	1	11%
Lack of efficacy determined by the PI	1	11%
TOTAL DC	**5/9**	**55%**

Four patients from the group of 12-14 years old group participated in the study until its closure.

Table 2 Discontinuation table of 15-18 years old patients detailing withdrawals over 72 months exposure:

DISCONTINUATION OF 15-18 YEARS OLD (AGE AT BASELINE) GROUP BY RESASON (N=76)		
Reason of DC	**Number of event**	**% Event of DC**
Lost to follow up	7	9%
Adverse events	7	9%
Sponsor discontinued study*	4	5%
Subject met withdrawal criteria*	19	25%
Investigator withdrew subject**	10	13%
Subject withdrew consent***	18	24%
Lack of efficacy as determined by PI	2	3%
TOTAL DC	**67/76**	**88%**

** A manually reviewed and identified that 20 of the patients who DC-ed due to one of these criteria due to aripiprazole having become locally commercially available.*

***The reasons of discontinuation by investigator are: patient non-compliance, exacerbation of symptoms, patient will no longer participate in clinical research, lack of compliance with birth-control,*

**** All cases were probed for unreported AEs. CSR-DREAS-Table 2 lists all AEs of the subjects who discontinued due to withdraw consent and used to cross-check any possible discontinuations due to AE.*

Table 3 describes the ages of patients at the time of their completion or termination of the study and it shows that 39 patients from the 85 (46%) were over 18 years old at the time of the study discontinuation.

Table 3 Descriptive Statistics for Age at Completion/Termination by Age at Baseline:

AGE AT BASELINE	AGE AT COMPLETION/ DISCONTINUATION	N	MEAN	SD	MEDIAN	MIN	MAX
12-14 YEARS OLD	15-18 YEARS OLD	5	16.4	1.5	16.0	15	18
	>18 YEARS OLD	4	19.0	0.0	19.0	19	19
	TOTAL	9	17.6	1.7	18.0	15	19
15-18 YEARS OLD	15-18 YEARS OLD	41	17.4	0.8	18.0	15	18
	>18 YEARS OLD	35	20.5	1.4	20.0	19	23
	TOTAL	76	18.8	1.9	18.0	15	23
TOTAL	15-18 YEARS OLD	46	17.3	0.9	18.0	15	18
	>18 YEARS OLD	39	20.3	1.4	20.0	19	23
	TOTAL	85	18.7	1.9	18.0	15	23

Nine patients (11%) from the group of 15-18 years old group participated in the study until its closure. A total of 20 (26.3%) patients had to discontinued due to the commercial availability of aripiprazole (sponsor discontinued study and subject met withdrawal criteria). For an average open-label global study for adolescent patients with the diagnosis of bipolar I disorder and/or schizophrenia the expected discontinuation date is 60% for 2 years while in study 31-03-243 58% of the patients discontinued for all reasons (with the exception of due to the drug availability in the country) which is a very high retention rate over a 5.5 years exposure.

MAH provided the tables of discontinuations as requested by the CHMP, however, MAH also wants to point out that the design of the study doesn't allow to observe the natural discontinuation of patients 20 (26.3%) who discontinued the study due to the commercial availability of aripiprazole in the country of participation. The study also has an unusually long exposure (up to 72 months) and during this time 46% of the patients became 18-23 years old.

Rapporteur comments:

Nine out of the 85 patients enrolled were aged 13-14 years at baseline (no patient was below 13). On the other hand 19 out of 85 were also already adults by the time of inclusion on study 31-05-243, since they reached adulthood in the parent study but were nevertheless eligible for inclusion in 31-05-243. Thus 55 patients were 15-18 years old at baseline when entering study 31-05-243; Nevertheless patients between 13 and 14 at baseline eventually reached 15 years old in less than 2 years, and therefore most conclusions of the overall population remain valid for the 15-18 YO population. Notwithstanding the above, a separate analysis of adolescents 15 through 18 was provided.

Withdrawal rate and causes of withdrawal were not significantly different. In the elder group, lack of compliance with birth control was considered a reason to discontinue by the investigator, but this is considered normal.

Issue solved.

Question 2

MAH should also further discuss weight gain and suicidality according to the EU relevant age range and their progression with treatment duration.

RESPONSE

Evaluation of weight

31 patients who were within the EU relevant age range, i.e. 15-18 years old at baseline, had potentially clinically relevant weight gain depending on an individual's change in height (or not) during that time period, i.e. more than 7% weight from baseline to the last visit with exposures up to 5.5 years. Table 4 shows the mean weight change from baseline and Table 5 the Mean BMI change from baseline for 15-18 years old patients at baseline.

Table 4 Mean Weight Change From Baseline for 15-18 Years Old Patients:

VITAL SIGN PARAMETER=WEIGHT (KG)

							CHANGE FROM BASELINE					
VISIT	n	MEAN	MEDIAN	SD	MIN	MAX	n	BASELINE MEAN	MEAN	MEDIAN	SD	MIN	MAX
BASELINE	76	62.15	58.35	15.87	39.00	129.00							
MONTH 6	67	62.65	60.00	16.50	36.00	136.00	67	61.47	1.18	1.10	3.25	-8.00	12.00
MONTH 12	58	63.76	59.70	16.37	39.00	136.00	58	61.21	2.56	2.17	4.10	-5.10	14.80
MONTH 18	50	64.96	61.00	17.50	45.00	137.00	50	61.27	3.69	2.90	5.47	-10.30	15.00
MONTH 24	38	66.65	61.25	19.56	45.00	140.00	38	63.08	3.57	2.80	5.67	-9.60	20.00
MONTH 30	24	69.73	61.50	23.63	45.00	145.00	24	64.19	5.54	5.05	7.59	-8.30	25.60
MONTH 36	19	69.33	62.00	24.20	47.00	143.00	19	62.71	6.62	3.30	7.19	-3.00	28.30
MONTH 42	14	68.20	61.50	25.30	46.00	143.00	14	61.25	6.95	4.70	7.11	0.00	26.20
MONTH 48	13	67.54	56.00	26.77	45.00	146.00	13	60.34	7.20	5.00	7.59	-3.00	24.10
MONTH 54	13	67.85	56.00	26.89	46.00	148.00	13	60.34	7.52	7.00	7.43	-5.00	20.60
MONTH 60	10	68.40	55.00	31.91	46.00	150.00	10	61.85	6.55	5.50	9.20	-10.00	21.00
MONTH 66	10	68.90	55.50	31.54	46.50	147.50	10	61.85	7.05	6.00	9.21	-10.50	20.20
MONTH 72	9	71.32	57.00	31.35	46.00	145.00	9	62.39	8.93	9.00	6.10	2.00	19.40
LAST VISIT	73	65.14	60.20	16.68	37.00	146.00	73	61.54	3.60	3.00	5.87	-10.50	19.40

Table 5 BMI - Mean Change From Baseline in 15-18 years old:

VITAL SIGN PARAMETER=BODY MASS INDEX (KG/M²)

							CHANGE FROM BASELINE					
VISIT	n	MEAN	MEDIAN	SD	MIN	MAX	n²	BASELINE MEAN	MEAN	MEDIAN	SD	MIN	MAX
BASELINE	76	22.44	21.35	4.26	15.50	35.40							
MONTH 6	67	22.46	21.50	4.52	15.10	37.30	67	22.22	0.24	0.20	1.20	-2.60	4.40
MONTH 12	58	22.80	21.75	4.60	14.50	37.30	58	22.25	0.55	0.50	1.44	-2.10	4.40
MONTH 18	50	22.92	21.70	4.67	16.10	37.60	50	22.19	0.73	0.70	1.93	-4.10	4.60
MONTH 24	38	23.33	22.15	5.19	17.00	38.40	38	22.76	0.57	0.55	2.07	-4.40	6.10
MONTH 30	24	24.60	22.75	6.05	17.70	39.70	24	23.34	1.27	0.85	2.49	-4.00	7.80
MONTH 36	19	24.51	22.20	5.94	18.30	39.20	19	22.91	1.60	0.90	2.21	-1.10	8.70
MONTH 42	14	25.46	24.15	5.42	19.20	39.20	14	23.37	2.09	1.80	2.24	-1.10	8.00
MONTH 48	13	24.83	23.40	5.59	18.80	40.00	13	22.60	2.23	2.20	2.23	-1.10	7.40
MONTH 54	13	24.92	23.70	5.53	18.60	40.60	13	22.60	2.32	2.10	2.29	-2.30	6.30
MONTH 60	10	24.57	24.10	6.51	17.30	41.10	10	22.41	2.16	1.80	2.91	-3.60	5.70
MONTH 66	10	24.77	24.00	6.34	17.10	40.40	10	22.41	2.36	2.70	2.95	-3.80	6.10
MONTH 72	9	25.64	24.30	5.81	19.60	39.70	9	22.58	3.07	3.90	1.73	0.90	5.90
LAST VISIT	73	23.02	21.80	4.54	15.20	40.00	73	22.31	0.71	0.60	1.98	-4.40	5.90

The mean weight change from baseline to endpoint increases over the 5.5 years exposure time as could be expected in a growing adolescent and young adult population. The mean change of BMI is below 1 until the 24 months visit, 1-2 during 24-36 months, 2-3 during 36-60 months and ~3 at 72 months. The mean BMI at entry was 22.44 (n=76) and even at Month 72 BMI is 25.63 which is above 25, which is considered to be the upper limit of the normal range in the remaining (n=9) patients. It should be noted that the number of patients decreased over time as many patients had to discontinue from the trial as aripiprazole became commercially available in their countries. Therefore, data on weight gain and BMI at the late stage of the trial were only representative of an extremely low number of patients and the data are hard to interpret.

Table 6 Weight Z-score - Mean Change From Baseline For 15-18 Years Old*:

								CHANGE FROM BASELINE				
VISIT	n	MEAN	MEDIAN	SD	MIN	MAX	n[a]	BASELINE MEAN	MEAN	MEDIAN	SD	MIN	MAX
BASELINE	76	-0.12	-0.09	1.23	-3.32	2.88							
MONTH 6	67	-0.20	-0.10	1.28	-4.35	3.04	67	-0.21	0.01	0.00	0.33	-1.03	1.28
MONTH 12	58	-0.11	-0.06	1.23	-4.41	3.05	58	-0.16	0.05	0.07	0.43	-1.33	1.22
MONTH 18	44	-0.12	0.02	1.18	-2.14	3.09	44	-0.20	0.08	0.12	0.51	-1.09	1.28
MONTH 24	25	-0.22	-0.03	1.18	-2.49	2.41	25	-0.16	-0.06	-0.01	0.53	-1.02	1.22
MONTH 30	14	-0.12	-0.18	1.14	-1.88	2.37	14	-0.23	0.10	0.01	0.66	-0.99	1.30
MONTH 36	9	0.18	-0.14	1.03	-0.74	2.19	9	-0.02	0.20	0.08	0.66	-0.61	1.39
MONTH 42	2	0.61	0.61	1.14	-0.20	1.42	2	0.08	0.53	0.53	1.01	-0.18	1.24
MONTH 48	1	-0.24	-0.24		-0.24	-0.24	1	-0.02	-0.22	-0.22		-0.22	-0.22
LAST VISIT	73	-0.15	-0.06	1.29	-4.08	3.09	73	-0.17	0.03	0.01	0.50	-1.00	1.24

**Weight Z scores could be calculated only up to 20 years of age; there are no patients below age 20 beyond Months 48.*

Due to the length of the trial and the natural growth of patients the weight Z scores are the most informative about the clinical relevance of the weight gain. Weight z-score is the deviation of a patient's weight from the mean weight of the reference population divided by the SD for the reference population. Weight z-score describes how similar a patient is to the population with the same age and the same gender by measuring the number of SDs from the expected weight, ie, how far away the patient's weight is from the population's mean weight.

Mean changes from baseline for weight z-scores within 0.5 SD of the general population is considered within normal limits for this population

The mean change of weight Z score shown in Table 4 varies between -0.22 to 0.12 SD which are clinically not significant except at Months 42 when the weight Z score is 0.53 SD. However at that point there are only 2 patients left in the group. Overall it could be concluded that the vast majority of study patients didn't show clinically significant shift from the expected age and gender appropriate weight trajectories.

Table 7 represents the shift of weight from baseline to every 6 months period of exposure up to 72 months between the following weight percentile categories: < 25%, 25 - <50%, 50 - <75%, 75 - <85%, 85 - <95%, >=95%. Due to the high rate of dropout the interpretation of data is difficult, therefore, we suggest to restrict the interpretation of data up to 24 months while the subject retention rate remains above 51%. We could observe that patients even with the longest exposures didn't tend to became obese, but there are too many patient discontinuations to make meaningful conclusions. Also the shift from baseline to last visit could be also informative and doesn't show a tendency for aripiprazole treated patients to become obese during treatment.

Table 7 Shift from Baseline in Weight Percentile by Visit (13-18 years old at baseline):

		PERCENTILE CATEGORY AT BASELINE											
		< 25%		25 - <50%		50 - <75%		75 - <85%		85 - <95%		>=95%	
VISIT	PERCENTILE CATEGORY AT THE VISIT	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%
MONTH 6	< 25%	21	(87.5)										
	25 - <50%	3	(12.5)	14	(66.7)	3	(20.0)						
	50 - <75%			7	(33.3)	7	(46.7)	2	(66.7)				
	75 - <85%					4	(26.7)	1	(33.3)	2	(40.0)		
	85 - <95%					1	(6.7)			3	(60.0)		
	>=95%											8	(100.0
MONTH 12	< 25%	15	(75.0)	2	(10.5)	1	(7.7)						
	25 - <50%	4	(20.0)	10	(52.6)	2	(15.4)						
	50 - <75%	1	(5.0)	7	(36.8)	7	(53.8)						
	75 - <85%					1	(7.7)	1	(50.0)	1	(20.0)		
	85 - <95%					2	(15.4)	1	(50.0)	4	(80.0)		
	>=95%												
	< 25%	13	(76.5)	3	(20.0)							6	(100.0)
MONTH 18	25 - <50%	3	(17.6)	3	(20.0)	2	(20.0)						
	50 - <75%	1	(5.9)	9	(60.0)	4	(40.0)	1	(25.0)				
	75 - <85%					3	(30.0)						
	85 - <95%					1	(10.0)	3	(75.0)				
	>=95%									5	(100.0)		
MONTH 24	< 25%	7	(77.8)	2	(25.0)								
	25 - <50%	2	(22.2)	2	(25.0)	1	(12.5)						
	50 - <75%			4	(50.0)	4	(50.0)	1	(33.3)				
	75 - <85%					2	(25.0)						
	85 - <95%					1	(12.5)	2	(66.7)				
	>=95%									3	(100.0)		
MONTH 30	< 25%	4	(66.7)	1	(20.0)								
	25 - <50%	2	(33.3)	1	(20.0)	2	(40.0)						
	50 - <75%			3	(60.0)	1	(20.0)	1	(100.0)				
	75 - <85%					1	(20.0)						
	85 - <95%					1	(20.0)						
	>=95%									3	(100.0)		
MONTH 36	< 25%			1	(20.0)								
	25 - <50%	3	(100.0)	2	(40.0)	2	(50.0)						
	50 - <75%			2	(40.0)	1	(25.0)						
	85 - <95%					1	(25.0)						
	>=95%							3	(100.0)				
MONTH 42	25 - <50%	1	(100.0)	1	(50.0)	1	(33.3)						
	50 - <75%			1	(50.0)	1	(33.3)						
	85 - <95%					1	(33.3)						
	>=95%							2	(100.0)				
MONTH 48	25 - <50%	1	(100.0)	1	(50.0)	1	(50.0)						
	50 - <75%					1	(50.0)						
	75 - <85%			1	(50.0)								
	>=95%							1	(100.0)				
MONTH 54	< 25%	1	(100.0)			1	(100.0)						
	50 - <75%			1	(100.0)								
	>=95%							1	(100.0)				
MONTH 60	< 25%	1	(100.0)			1	(100.0)						
	50 - <75%			1	(100.0)								
	>=95%							1	(100.0)				
MONTH 66	< 25%	1	(100.0)			1	(100.0)						
	50 - <75%			1	(100.0)								
	>=95%							1	(100.0)				
MONTH 72	< 25%	1	(100.0)			1	(100.0)						
	50 - <75%			1	(100.0)								
LAST VISIT	< 25%	19	(73.1)	5	(23.8)	2	(12.5)						
	25 - <50%	6	(23.1)	8	(38.1)	1	(6.3)						
	50 - <75%	1	(3.8)	8	(38.1)	8	(50.0)	1	(25.0)	1	(14.3)		
	75 - <85%					3	(18.8)			1	(14.3)		
	85 - <95%					2	(12.5)	3	(75.0)	5	(71.4)		
	>=95%											8	(100.0)

Overall, 37/82 subjects (45.1%) had a potentially clinically significant increase in weight (7% increase compared to baseline) and 4/82 subjects (4.9%) had a potentially clinically significant decrease in weight (7% decrease compared to baseline) at the last visit of the trial. Overall, mean changes from baseline to the last visit for weight z-scores were within 0.53 of the general population and changes from baseline were negligible.

Evaluation of suicidal cases

Four (of 85) subjects experienced a suicide-related TEAE, including events of suicide attempt (3 subjects) and intentional self-injury (1 subject). All 3 events of suicide attempt were considered serious, and 2 of these 3 led to discontinuation of trial medication. One subject recorded a positive

response on the C-SSRS (reported as TEAE of intentional self-injury). One patient was 21 years old at the time of the event of self-injurious behaviour around 3 years after study entry and after resolution of the event he continued the study for approximately two more years. One patient was over 18 years old at the time of the suicidal attempt and two patients were 15 years old. The study exposure in study 31-03-243 is listed in Table 8, however, patients were rolled over from a parent study where they were also exposed to aripiprazole. Three of the events assessed by PI as not related to study drug and one as probably not related to study drug. Two of the events occurred around a year or more during the study exposure what would be also atypical for drug induced suicidal events.

Table 8 Listing of Adverse Events Related to Suicidal Ideation/Suicide:

SUBJECT ID	AGE/SEX/RACE	TOTAL EXPOSURE (DAYS)	AGE AT AE ONSET	AE(MEDDRA PT[2]/ VERBATIM TERM)	AE STUDY DAY§	AE DURATION (DAYS)
1522065	17/M/CAUC.	2030	21	INTENTIONAL SELF-INJURY (A)/ SELF HARM BEHAVIOR	1400	1
3603063	17/M/ASIAN	326	18	SUICIDE ATTEMPT (AB)/ SUICIDAL ATTEMPT	339	3
3623035	15/F/ASIAN	80	15	SUICIDE ATTEMPT (ABE)/ SUICIDE ATTEMPT	78	1
7013041	15/F/OTHER	25	15	SUICIDE ATTEMPT (ABE)/ SUICIDE ATTEMPT	26	1

Subject 05243-152-2065

Subject 05243-152-2065, a 17 year-old Caucasian male diagnosed with schizophrenia on December 6, 2004 began receiving aripiprazole 20 mg on Study Day 1/ 23-Nov-2006. The subject was enrolled in an open-label, rollover study for subjects with schizophrenia completing aripiprazole clinical study 31-03-241. Medical history included intraventricular conduction defect, left cardiac circumflex hypertrophy, mild unstable hypertension, obesity, elevated insulin levels, and herpangina. Approximately at Month 50 (Day 1400), the subject experienced self-injurious behaviour that reported ending the same day. The subject was taking 20 mg of study medication at the event onset. No action was taken with the study medication at the time of the adverse event. Per the Children's Depression Rating Scale – Revised (CDRS-R) assessment for suicidal ideation at Screening in the parent study 31-03-239, the subject had thoughts about suicide, especially when angry. No adverse events were ongoing at the time of the self-harm behaviour event. No concomitant medications were taken within 14 days prior to the self-harm behaviour event. The subject completed the 31-05-243 study at Month 72 (Day 2030). There was no action taken with the study medication in regards to the event. No concomitant medications were taken within 14 days prior to the event. There were no clinically significant laboratory tests relevant to the event. The investigator assessed the event as mild in severity and not likely related to the study medication. The sponsor assessed the event as unrelated to the study medication.

Subject 05243-360-3063

Subject 05243-360-3063, a 17 year-old Asian male diagnosed with schizophrenia on December 1, 2004 began receiving aripiprazole 20 mg on Study Day 1/ 22-Jan-2007. The subject was enrolled in an open-label, rollover study for subjects with schizophrenia completing aripiprazole clinical study 31-03-241. Medical history included mitral valve prolapse - AML Grade 1".

On Study Day 327/ 14-Dec-2007, the subject was removed from the study by the investigator due to protocol non-compliance. On Study Day 339/ 26-Dec-2007, 12 days after discontinuation of the study medication, the subject experienced a serious event of suicide attempt. The subject had a quarrel with

his wife over a trivial issue and consumed an unknown amount of unidentifiable tablets in an attempted suicide. The subject was immediately taken to the hospital for further treatment and evaluation. On Study Day 341/ 28-Dec-2007, the event resolved and the subject was discharged from the hospital in stable condition. There was no action taken with the study medication in regards to the event as it had been discontinued prior to event onset. The investigator assessed the event to be moderate in severity and unrelated to the study medication. The sponsor assessed the event as unrelated to the study medication. No concomitant medications were taken within 14 days prior to the event. There were no clinically significant laboratory tests relevant to the event.

Subject 05243-362-3035

Subject 05243-362-3035, a 15 year-old Asian female diagnosed with schizophrenia in 2004 began receiving aripiprazole 10 mg on Study Day 1/ 30-Nov-2006. The subject was enrolled in an open-label, rollover study for subjects with schizophrenia completing aripiprazole clinical study 31-03-241. Medical history included increased glucose level and increased insulin level.

On Study Day 78/ 15-Feb-2007, the subject experienced a serious event of suicide attempt. The subject attempted to commit suicide by trying to jump off a bridge near her home. The subject climbed on the wall of a bridge and was about to jump when a bystander stopped her. The subject was immediately taken to the investigator site for further evaluation and treatment. The subject was treated with oral chlorpromazine, fluoxetine, and risperidone and responded well. The study medication was discontinued due to the event and the last dose was taken on Study.

Day 80/ 17-Feb-2007. The subject was taking 20 mg of study medication daily at the event onset. Concomitant medications taken within 14 days prior to the event included alprazolam, amitriptyline, and sertraline. There were no clinically significant laboratory tests relevant to the event. The investigator assessed the event to be moderate in severity and not likely related to the study medication. The sponsor assessed the event as not likely related to the study medication.

Subject 05243-701-3041

Subject 05243-701-3041, a 15 year-old Hispanic/Latino female diagnosed with schizophrenia in December 2005 began receiving aripiprazole 30 mg on Study Day 1/ 14-Dec-2006. The subject was enrolled in an open-label, rollover study for subjects with schizophrenia completing aripiprazole clinical study 31-03-241. The subject has no known medical history.

On Study Day 26/ 08-Jan-2007, the subject experienced a serious event of suicide attempt. The subject reportedly ingested an unknown amount of aripiprazole tablets and 4 tablets of estralazine (10 mg). The subject was taken to the hospital for further evaluation and treatment. The subject was treated with oral lithium and responded well.

On the same day Study Day 26/ 08-Jan-2007, the event resolved and the subject was discharged from the hospital in stable condition. The study medication was discontinued due to the event and the last dose was taken on Study Day 25/ 07-Jan-2007. The subject was receiving 30 mg of aripiprazole at the time of event onset. Concomitant medications taken within 14 days prior to the event included clonazepam. There were no clinically significant laboratory tests relevant to the event. The investigator assessed the event to be severe in severity and unrelated to the study medication. The sponsor assessed the event as not likely related to the study medication.

Conclusion on Question 1 + Question 2

Study 31-05-243 was a medication access study of aripiprazole on a compassionate use basis to adolescents and adults with schizophrenia after the completion of study 31-03-241 or 31-03-239 up to 72 months or until aripiprazole became available in the country of participation. As a result of this, 20

patients of 85 (26.3%) got discontinued due to the local commercial availability of aripiprazole. The artificial discontinuation of patients due to the local commercial availability makes it very difficult to interpret the patient discontinuations. The long-term weight changes also hard to interpret due to the low number of patients after Months 24 visit. Based on the explanation provided above MAH suggests a cautious interpretation of data beyond Month 24 for this uncontrolled compassionate use study.

Rapporteur comments:

Weight gain

It is agreed that weight gain cannot be assessed *per se* because adolescents at this age are also growing, and weight gain is expected. Therefore the BMI change is much more important. It should also be mentioned that schizophrenic patients frequently have lower BMI than the average adolescent population, and that BMI in adolescents is usually also lower than in adults. Therefore the readings on BMI should be viewed cautiously. To counterbalance this - as discussed above - half of enrolled subjects had reached adulthood when terminating the study.

Whilst on an average and median basis the BMI increase was not considered significant, for an increase of 3 points in BMI may be acceptable when reaching adulthood and with disease control, the patients that were on the higher limit and have increased from 4.6 points on Mth 18 until 8.7 BMI points on Mth 36, have surely increased weight with clinical significance. This is also confirmed by the net weight increase up to 28.3 Kg also on Mth 36. The mean change of weight Z score, which is usually useful to follow the progression of weight increase, does not help due to the low number of patients and the drop out rate.

The weight increase has been described in the SmPC for adolescents. Although it has not been so strikingly expressed for schizophrenia as it has been for bipolar disorder type 1, the fact is that the robustness of the data presented now is lower than the data presented for BD. Therefore we do not propose a change to SmPC.

Suicidality

There were 4 suicidal related events. One was a self-injury behaviour lasting one day, and the other three were suicidal attempts: two with medication and one aborted suicide (jumping off a bridge). Two of them were considered not likely related to study drug by the investigator and were downgraded to not related by the sponsor; one was considered not related by the investigator and was upgraded to not likely related by the sponsor; the most problematic episode (Subject 05243-362-3035, jumping off a bridge) was considered by the investigator as moderate in severity, and not likely related to the study medication - the sponsor assessed the event as not likely related to the study medication. Analysis of the reported event does not seem as benign as it was described and rated.

Suicidality is already expressed in SmPC, and has been reinforced with variation II-84. The data presented now consubstantiates the last proposed wording on suicidality in section 4.4: "*There are insufficient paediatric data to evaluate this relative risk in younger patients (below 18 years of age), but there is evidence that the risk of suicide persists beyond the first 4 weeks of treatment for atypical antipsychotics, including aripiprazole*." Therefore no further comments are considered.

Issue solved.

Question 3

The data presented for the long term study in children and adolescents with schizophrenia do not reveal previously unknown events or weaning of efficacy in this aripiprazole responder population.

However, the frequency of some events should be further discussed and detailed in the EU relevant age group (15-18 years), such as weight gain and suicidality. This discussion should also consider the need to update RMP for these aspects.

RESPONSE

The potential risks of Suicide related events and Weight gain are adequately described in the current RMP. As discussed in the latest RMP update (V 8.0) submitted on 06 May 2013, the risk minimization measures include a description of the potential risks of Suicide related events and Weight gain in the Warnings & Precautions, section 4.4 and Undesirable effects, section 4.8 of the SmPC. MAH believes that the description of these events is adequate and there is no need for a further update to the RMP.

Rapporteur comments:

Agreed. Please see comments from questions 1 and 2 above.

Issue solved.

Question 4

As for previous studies, the frequency of low prolactinaemia should be appended to section 4.8 of SmPC, such as:

"In the paediatric (13-17 years) schizophrenia population with aripiprazole exposure of 5 to 30 mg up to 72 months, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 25.6% and 45.0%, respectively."

RESPONSE

The current SmPC, section 4.8, provides the following information based on placebo-controlled trials:

"*Schizophrenia in adolescents aged 15 years and older*

[...]

In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 29.5% and 48.3%, respectively."

MAH would like to caution with the interpretation of low prolactin levels up to 72 months from the roll-over study 31-05-243 due to the very low number of patients represented at that time. Only 13 patients out of 85, which represents the 14% of the patients reached the Months 72 study visit. The lack of control group adds another layer of difficultly to the interpretation of prolactin data in this study.

Overall Conclusion

Long-term administration of open-label aripiprazole was generally safe and no new AEs of concern were identified. The study data is commensurate with the aripiprazole data already described in the SmPC and the description of suicidality and weight-gain is adequately addressed in the current RMP.

Rapporteur comments:

The study constraints are understood, but do not significantly diverge from other longterm follow up studies. This data also goes along with the previous statement in the SmPC, but clearly extends the impact from 2 to 5 years, with a similar (if not higher) rate of exposed patients. Therefore we consider that appending the proposed sentence to SmPC is valid. Another argument that justifies the new sentence is the fact that hypoprolactinaemia lasting for 5 years in this population will transport this effect into early adulthood. There is a biological plausibility that a lower prolactinaemia may increase fertility in these patients, and this aspect should be taken into consideration when planning treatment for schizophrenic patients.

The proposed sentence to be appended on SmPC is still considered to be needed.

Updated Rapporteur's overall conclusion and recommendation

The data presented with the stratification of ages at study entrance in the EU relevant age group (15 - 18 years) in adolescents with schizophrenia did not reveal a different pattern of events or weaning of efficacy from the overall results. Drop out rates, weight gain and suicidality did not behave differently. The response to the proposal of a new sentence on low prolactinaemia levels however, is not agreed upon. Unlike the MAH, the importance of a new sentence is considered significant as to be appended to SmPC. Fertility and unexpected pregnancies are already dealt with in RMP, and as for the other aspects (weight gain, suicidality) there is no need to update RMP for these aspects.

In conclusion, the frequency of low prolactinaemia should be appended to section 4.8 of SmPC:
"In the adolescent (13-17 years) schizophrenia population with aripiprazole exposure of 5 to 30 mg up to 72 months, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 25.6% and 45.0%%, respectively."