15 September 2016
EMA/702260/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abilify

International non-proprietary name: aripiprazole

Procedure No. EMEA/H/C/000471/II/0110

Note

Variation 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 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the procedure 4
1.1. Type II variation 4
1.2. Steps taken for the assessment of the product 4
2. Scientific discussion 5
2.1. Introduction 5
2.2. Non-clinical aspects 7
2.2.1. Ecotoxicity/environmental risk assessment 7
2.2.2. Conclusion on the non-clinical aspects 8
3. Clinical aspects 8
3.1. Clinical efficacy 8
3.1.1. Main study(ies) 8
3.1.2. Discussion on clinical efficacy 31
3.1.3. Conclusions on the clinical efficacy 31
3.2. Clinical safety 31
Introduction 31
3.2.1. Discussion on clinical safety 50
3.2.2. Conclusions on clinical safety 50
3.2.3. PSUR cycle 51
3.3. Update of the Product information 51
4. Benefit-Risk Balance 52
5. Recommendations 53
6. EPAR changes ..... Error! Bookmark not defined.

List of abbreviations

AE	Adverse Events
CGAS	Children's Global Assessment Scale
CGI-S	Clinical Global Impression - Severity
EPS	Extrapyramidal symptoms
ERA	Environmental Risk Assessment
IDMC	Indipendent Data Monitoring Committee
IMS	Institut für Medizinische Statistik
IVRS	Interactive voice response system
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version
LOCF	Last Observation Carried Forward
NY-AACENT	New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment
PEC	Predicted Environmental Concentration
PIP	Paediatric investigation plan
PNEC	Predicted No-Effect Concentration
PANSS	Positive And Negative Syndrome Scale
SmPC	Summary of Product Characteristics

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Otsuka Pharmaceutical Europe Ltd submitted to the European Medicines Agency on 3 March 2015 an application for a variation.

The following variation was requested:

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

Extension of Indication to include treatment of schizophrenia in adolescents between 13 – 15 years of age based on paediatric studies 31-09-266 and 31-09-267 submitted according to Article 46 of the paediatric regulation. As a consequence, sections 4.1, 4.2 and 4.8 of the SmPC were proposed to be updated and the Package Leaflet was proposed to be updated accordingly.

Information on paediatric requirements

Not applicable

Article 8 of the paediatric regulation does not apply to this application, since the authorised medicinal product is not protected by a supplementary protection certificate under Regulation (EC) No 469/2009 or by a patent which qualifies for the granting of the supplementary protection.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Bruno Sepodes Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	3 March 2015
Start of procedure	27 June 2015
CHMP Rapporteur Assessment Report	25 August 2015
CHMP members comments	14 September 2015
Updated CHMP Rapporteur Assessment Report	18 September 2015
1st Request for supplementary information (RSI)	24 September 2015
MAH response	22 December 2015
CHMP Rapporteur Assessment Report	8 February 2016
CHMP members comments	15 February 2016
2nd Request for supplementary information (RSI)	25 February 2016
MAH response	22 April 2016
CHMP Rapporteur Assessment Report	31 May 2016
CHMP members comments	13 June 2016
3rd Request for supplementary information (RSI)	23 June 2016
MAH response	15 August 2016
CHMP Rapporteur Assessment Report	1 September 2016
CHMP members comments	8 September 2016
Updated CHMP Rapporteur Assessment Report	N/A
CHMP Opinion	15 September 2016

2. Scientific discussion

2.1. Introduction

The applicant submitted a type II variation application to propose changes in SmPC sections 4.1 and 4.2 regarding the treatment of schizophrenia in adolescents from “aged 15 years and older” to “aged 13 years and older”, and the corresponding changes in SmPC section 4.2 from “below 15 years” to “below 13 years” and the package leaflet as a new therapeutic indication (extension of target population for the same disease, based on a different age range).

In general, there is consensus that schizophrenia is a severe psychiatric disorder both in childhood and adolescence as well as in adulthood. The lifetime prevalence of schizophrenia is approximately 1%. It is assumed that only 0.1 to 1% of all schizophrenic psychoses manifest themselves before the age of 10, and 70% of all schizophrenic disorders occur between the age of 20 and 45 (Remschmidt & Theisen, 2005).

The prevalence rate of very early-onset schizophrenia (manifestation before the age of 12) is less than one child in 10,000 children between 2 and 12 years of age (Burd & Kerbeshian, 1987). It is estimated that childhood-onset schizophrenia is approximately 50 times less frequent than adult-onset schizophrenia. There is a remarkable increase of schizophrenia after the 13th year of life (Remschmidt et al., 1994), and the prevalence of schizophrenia among adolescents has been estimated to be as high as 0.5% (Gillberg et al, 1986).

The course of the disease in the adolescent population is variable. Some adolescents with schizophrenia experience only one cycle of these phases, although most have multiple cycles (McClellan et al, 1993; Werry et al, 1991). The long-term outcome of adolescents diagnosed with schizophrenia has been studied by several investigators and psychiatrists in follow-up studies. In the majority of cases schizophrenia turned out to be a chronic or relapsing disorder with only a minority of patients that were fully employed or were attending school full-time (Werry et al, 1991; Tsai & Champine, 2004).

In a published retrospective study (Krausz & Muller-Thomsen, 1993), only 37% and 42% of patients had no symptoms and no findings after follow-up examinations at 5 years and 11 years, respectively. Moreover, 21% and 20% of the patients were hospitalized for the entire 6 months preceding the follow-up examinations at 5 and 11 years, respectively.

Aripiprazole is an atypical antipsychotic that is approved via the 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)

This assessment of extension of indication discusses the results of two completed clinical trials that address 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:

- Trial 31-09-266: A phase 3 long-term multicentre, randomised, double-blind, placebo-controlled study enrolling patients in the US, Russia, Romania, India, Philippines, Malaysia, and Taiwan to evaluate the efficacy, safety, and tolerability of aripiprazole as maintenance treatment in adolescent patients aged 13 to 17 years with schizophrenia.
- Trial 31-09-267: A Long-term, multicentre, open-label Study to evaluate the Safety and Tolerability of flexible-dose oral Aripiprazole (OPC-14597) as Maintenance Treatment in Adolescent Patients with Schizophrenia or Child and Adolescent Patients with Bipolar I Disorder, Manic or mixed Episode with or without Psychotic Features

Trial 31-09-267 was conducted as a post-approval commitment to the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) and was later added to the Abilify Schizophrenia PIP by the Paediatric Committee (PDCO) of the EMA.

The focus of the submission is:

- To compare the safety results for the use of aripiprazole in Trial 31-09-267 in younger paediatric subjects (ages 10 to 14 years) with safety results in older paediatric subjects (ages 15 to 17 years);

- To demonstrate the safety of aripiprazole in Trial 31-09-267 for selected safety topics required by the CHMP and PDCO, ie, sexual maturation and growth (Tanner Staging), cognitive adverse effects assessed using the New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT), special interest adverse events (AEs) relating to sedation/somnolence, and special interest AEs relating to metabolic measures (i.e., glucose, weight gain, and prolactin).

2.2. Non-clinical aspects

2.2.1. Ecotoxicity / environmental risk assessment

The present variation concerns a new therapeutic indication for the paediatric population. ABILIFY will be indicated for the treatment of schizophrenia in adolescents **aged 13 years** and older. A complete environmental risk assessment (ERA) was previously assessed and approved for aripiprazole; a $PEC_{surfacewater}$ of 0.15 µg/L calculated with a default Fpen of 0.01/DOSEai of 30 mg and a PEC/PNEC below 1 (0.58) were obtained.

For the current type II variation the applicant presented two exposure approaches:

a) With Prevalence data (total population – adult and paediatric)

Two different values for $PECs_{urfacewater}$ based on refined Fpen calculations of prevalence data for the sought indication: 0.5% and **2.2 %** as median and highest prevalence of schizophrenia were determined. The PNEC resulted from the toxicity and environmental fate studies already performed and approved for the medicinal product marketing authorisation.

The most conservative PEC/PNEC ratios compared with the previously approved environmental exposure are summarised below. Some results (in bold) were corrected by the assessor, since the applicant in its ERA report considered wrongly these values.

Exposure values	prevalence data 0.5%	prevalence data 2.2 %	Previously approved exposure
$PEC_{surfacewater}$	0.057 µg/L	**0.251 µg/L**	0.15 µg/L
PEC/PNEC surfacewater	0.057 / 0.261 = 0.218	**0.251 / 0.261 = 0.962**	0.15 / 0.261 = 0.58

b) With Sales / Forecast data (total population – adult and paediatric)

Based on the IMS sales data of aripiprazole (2011–2013) was concluded that 386692 person/year (who received 15 mg daily) were treated with aripiprazole. This stands for 8.8% of 4.4 million adults with schizophrenia. Taking the highest prevalence of 2.2%, the applicant calculated 96800 new cases / year of which 5.2% (5033) are adolescent between 10-14 years of age.

The forecast consummation data for the year 2019 was estimated as 3801.31 Kg (growth rate of ~9%). A refined PEC of 0.000764 µg/L and a ratio $PEC/PNEC_{surfacewater}$ of 0.003 were determined taking into account a Fpen based on this estimated consummation data and the total population for EU in 2020.

During the procedure, the applicant was requested to discuss the possible significant environmental exposure conditioned by the increase of the therapeutic use (adolescents in the 13-15 age range). The applicant updated the ERA and PEC /PNEC ratios were recalculated taking into account the addition of both PECs surface water: paediatric population and adult / adolescent population. Having reviewed the data, the

CHMP concluded that no significant increase of environmental exposure to this medicinal product was to be expected.

The questions posed by the assessor have been adequately addressed.

2.2.2. Conclusion on the non-clinical aspects

Considering the above data, aripiprazole should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

3. Clinical aspects

3.1. Clinical efficacy

3.1.1. Main study(ies)

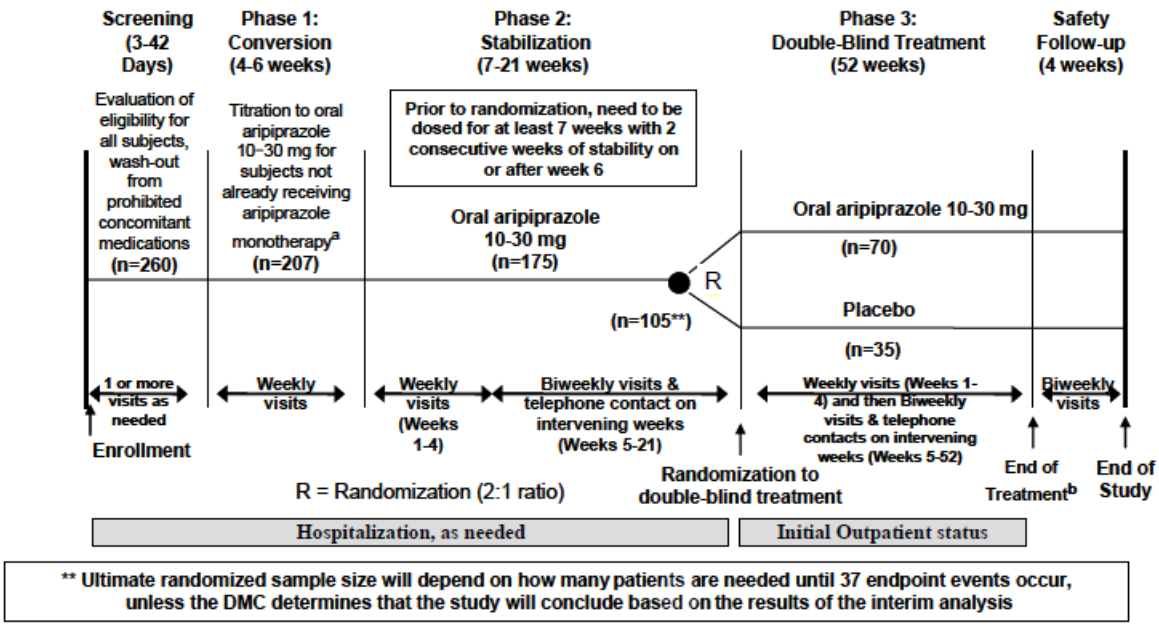
The efficacy information submitted in this application is provided by 2 long-term trials, Trial 31-09-266 and Trial 031-09-267.

Study 31-09-266

A Long-Term Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Aripiprazole (OPC-14597) as Maintenance Treatment in Adolescent Patients with Schizophrenia.

Methods

This was a placebo-controlled relapse-prevention trial conducted in the US, Russia, Romania, India, Philippines, Malaysia, and Taiwan. Trial 31-09-266 had a screening period, three phases (Conversion, Stabilization, and Double-blind Maintenance), and a follow-up period. The duration of this trial from first subject enrolled to last subject completed was approximately 5 years, including a 3-year recruitment period. Individual participation for subjects, who completed the trial, ranged from a minimum of approximately 60 weeks to a maximum of 89 weeks. Length of participation varied depending on the screening duration (3 to 42 days), the time required for conversion to aripiprazole monotherapy (0 to 6 weeks), the time required to achieve stability on oral aripiprazole (7 to 21 weeks), the duration of maintenance prior to any possible exacerbation of psychotic symptoms (up to 52 weeks), and the need for 4-week post-trial follow-up.



Schematic representation of the design for trial 31-09-266

Study participants

Eligible subjects were male or female adolescent, aged 13 to 17 years, who met the current diagnostic criteria of schizophrenia, as defined by DSM-IV-TR criteria and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL), and a history (as per subject, family, or healthcare provider, or by previous medical records) of the illness (diagnosis or symptoms) for at least 6 months prior to screening, and were able to comply with protocol requirements. Subjects were excluded from the trial based on a significant risk of committing suicide based on history (e.g., suicide attempt in the past 1 year) or routine psychiatric status examination or met DSM-IV-TR criteria for substance dependence (including alcohol and benzodiazepines, but excluding caffeine and nicotine) within 180 days prior to screening.

Treatments

Conversion:

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.

Stabilisation:

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) the subject was being treated with oral aripiprazole monotherapy between 10 mg/day to 30 mg/day or

(3) 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.

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.

Maintenance:

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.

Follow-up:

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.

Objectives

The primary objective of the trial was to evaluate the efficacy of aripiprazole compared with placebo in adolescent schizophrenic subjects who had maintained stability on oral aripiprazole for 2 consecutive weekly time points after at least 7 weeks of treatment.

The secondary objective was to evaluate the safety and tolerability of oral aripiprazole as maintenance treatment in adolescent subjects with schizophrenia.

Outcomes/endpoints

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

Sample size

The expected total number of exacerbations of psychotic symptoms/impending relapse was estimated using a 2:1 (aripiprazole: placebo) randomization ratio to achieve at least 80% power and to preserve an overall nominal alpha level of 0.05 (2-sided). The resulting total number of events satisfying these design constraints was 37, assuming 52-week relapse rates of 66% for placebo and 33% for aripiprazole, corresponding to a hazard ratio of 0.37 (aripiprazole vs placebo) and an exponential distribution for relapse times.

An interim analysis was performed after the accrual of approximately 75% of endpoints (=28), and the final analysis at 100% of planned events (=37). Hence, the target number of events was 28 for the interim analysis. This event-driven trial was terminated by the sponsor after the 37th exacerbation of psychotic symptoms/impending relapse was confirmed. The O'Brien-Fleming group sequential boundaries were used to allocate alpha levels of 0.019 to the interim look, and 0.044 to the final analysis. It was expected that 105 subjects would be randomized, in a 2:1 ratio (70 in the aripiprazole group and 35 in the placebo group) to yield 37 events. The planned sample size and power assumed a 52-week dropout rate for reasons other than relapse of 30% and an accrual period of 1 day followed by trial duration of 52 weeks, in addition to the

assumptions applied to estimate the required number of events. The statistical computing software EAST was utilized in the sample size calculations.

Before a protocol amendment, the sample size calculation was based on 90% power and on two interim analyses, and the number of events needed was 49.

Randomisation

Upon meeting entry requirements into the double-blind maintenance phase, subjects were assigned to trial medication via an interactive voice response system (IVRS) or interactive web response system (IWRS) according to a computer generated randomization code provided by the sponsor.

Blinding (masking)

During the double-blind phase of the trial, the treatment assignment code list was available only to an independent biostatistician and the clinical supply operations group. Subjects, investigational site personnel, the sponsor's employees, and all other trial personnel remained blinded to the identity of the treatment assignments until every subject had completed trial treatment and the database was locked.

There was a planned interim analysis, and the results of the interim analysis and individual subject data remained blinded to the sponsor during the course of the IDMC's unblinded data analysis.

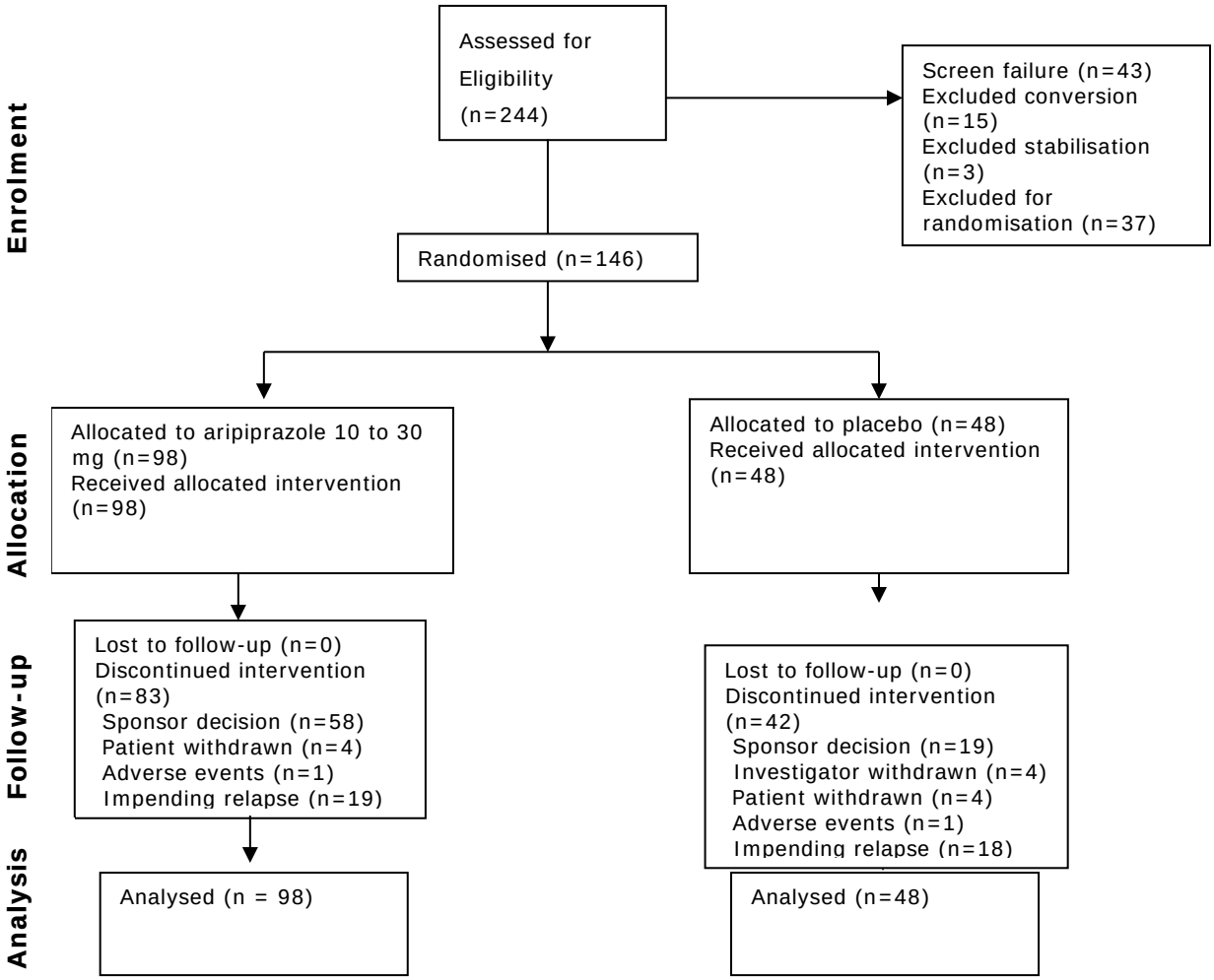
Statistical methods

The primary efficacy analysis compared the efficacy of oral aripiprazole (10 to 30 mg/day) with that of placebo with regard to time to exacerbation of psychotic symptoms/impending relapse in the Double-Blind Maintenance Efficacy Sample. The primary efficacy endpoint was analysed using a log rank test comparing the 2 treatment groups at an overall nominal significance level of 0.05 (2-sided) following a group sequential procedure. The interim analysis was performed after approximately 75% of endpoints had accrued using O'Brien-Fleming sequential boundaries with an alpha level of 0.0193 for rejecting the null hypothesis at the interim time. The alpha level for the final analysis was 0.0442. Additionally, the corresponding confidence intervals for the hazard ratio (aripiprazole vs placebo) for the interim and final analyses were provided using the Cox proportional hazard model with terms for treatment in the model. Analyses of the secondary and other efficacy endpoints were performed for the Doubleblind Maintenance Phase Efficacy Sample using both last observations carried forward (LOCF) and observed cases (OC) datasets. Efficacy endpoints in the form of mean change from baseline were summarized by descriptive statistics and compared between the aripiprazole and placebo groups by fitting an analysis of covariance (ANCOVA) model to the change scores with terms for treatment as a factor and baseline value as a covariate. Mixed models for repeated measures (MMRM) were employed to compare the change scores between the aripiprazole and placebo groups. Mean CGI-I score at endpoint was summarized by descriptive statistics and compared between the aripiprazole and placebo groups using the Cochran-Mantel-Haenszel method based on row mean score statistics. Proportion endpoints were summarized by counts and percent's and, in addition, compared between the aripiprazole and placebo groups by the Chi-square test. Time to discontinuation due to all causes was compared between the aripiprazole and placebo groups using the log rank test, along with Kaplan-Meier curves. The secondary and other efficacy endpoints at the end of the stabilization phase were evaluated using descriptive statistics for the Stabilization Efficacy Sample.

Results

Participant flow

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, see below for details on the participant's flow).



Baseline data

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, 41 (28.8%) 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. A minority (12.3%) of subjects in Trial 31-09-266 were enrolled at trial sites in an EU member country (Romania), the others were enrolled from outside the EU.

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 was 86.9) and the double-blind maintenance phase where n = 146 subjects (mean was 65.5 in the aripiprazole group and 62.9 in the placebo group). There was a decrease in mean CGI-S scores in the double-blind maintenance phase for both treatment groups (3.2 in the aripiprazole group and 3.0 in the placebo group) relative to the larger group treated in the conversion phase. The mean CGAS score increased in the double-blind maintenance phase in both treatment groups (60.9 in the aripiprazole group and 66.1 in the placebo group). The table below shows the study participant demographics:

Table 2.7.3.3.1.2-1 Demographics (Enrolled Sample)

	Conversion			Stabilization			Double-blind Maintenance			Total		
Demographic Characteristics	**Males N = 124**	**Females N = 62**	**Total N = 186**	**Males N = 120**	**Females N = 63**	**Total N = 183**	**Males N = 96**	**Females N = 50**	**Total N = 146**	**Males N = 133**	**Females N = 68**	**Total N = 201**
Age (Years)												
N	124	62	186	120	63	183	96	50	146	133	68	201
Mean (SD)	15.1 (1.2)	15.2 (1.1)	15.1 (1.2)	15.2 (1.2)	15.2 (1.1)	15.2 (1.2)	15.4 (1.2)	15.3 (1.1)	15.4 (1.2)	15.1 (1.2)	15.2 (1.1)	15.1 (1.2)
Weight (kg)												
N	124	62	186	120	63	183	95	49	144	133	68	201
Mean (SD)	62.10 (17.10)	56.50 (14.40)	60.20 (16.40)	63.50 (17.20)	57.40 (14.00)	61.40 (16.40)	65.20 (17.20)	58.80 (12.70)	63.10 (16.10)	63.00 (17.30)	56.90 (14.20)	60.90 (16.50)
Height (cm)												
N	124	62	186	120	63	183	96	49	145	133	68	201
Mean (SD)	167.1 (10.7)	158.8 (8.4)	164.3 (10.7)	168.0 (10.7)	158.5 (8.2)	164.7 (10.9)	169.2 (10.4)	158.9 (8.1)	165.7 (10.8)	167.4 (10.6)	158.4 (8.2)	164.4 (10.7)
BMI												
N	124	62	186	120	63	183	94	48	142	133	68	201
Mean (SD)	22.0 (4.6)	22.3 (5.1)	22.1 (4.7)	22.2 (4.5)	22.8 (4.9)	22.4 (4.7)	22.5 (4.6)	23.3 (4.7)	22.8 (4.7)	22.2 (4.6)	22.6 (5.0)	22.3 (4.7)
BMI (kg/m^2)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
<18.5	21 (16.9)	13 (21.0)	34 (18.3)	17 (14.2)	8 (12.7)	25 (13.7)	11 (11.5)	5 (10.0)	16 (11.0)	21 (15.8)	13 (19.1)	34 (16.9)
18.5 - <25	84 (67.7)	34 (54.8)	118 (63.4)	84 (70.0)	36 (57.1)	120 (65.6)	65 (67.7)	28 (56.0)	93 (63.7)	89 (66.9)	36 (52.9)	125 (62.2)
25 - <30	11 (8.9)	10 (16.1)	21 (11.3)	10 (8.3)	14 (22.2)	24 (13.1)	12 (12.5)	9 (18.0)	21 (14.4)	13 (9.8)	13 (19.1)	26 (12.9)
≥ 30	8 (6.5)	5 (8.1)	13 (7.0)	9 (7.5)	5 (7.9)	14 (7.7)	6 (6.3)	6 (12.0)	12 (8.2)	10 (7.5)	6 (8.8)	16 (8.0)
Race	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
White	73 (58.9)	35 (56.5)	108 (58.1)	75 (62.5)	37 (58.7)	112 (61.2)	61 (63.5)	30 (60.0)	91 (62.3)	80 (60.2)	39 (57.4)	119 (59.2)
Black or African American	1 (0.8)	0 (0.0)	1 (0.5)	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.5)
Asian	49 (39.5)	25 (40.3) 2 (3.2)	74 (39.8)	43 (35.8)	25 (39.7) 1 (1.6)	68 (37.2)	34 (35.4) 1 (1.0)	20 (40.0) 0 (0.0)	54 (37.0)	51 (38.3)	27 (39.7) 2 (2.9)	78 (38.8) 3 (1.5)
Other	1 (0.8)	3 (1.6)		1 (0.8)		2 (1.1)			1 (0.7)	1 (0.8)		
Ethnicity[a]	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Hispanic or Latino	6 (4.8)	1 (1.6)	7 (3.8)	7 (5.8)	2 (3.2)	9 (4.9)	5 (5.2)	2 (4.0)	7 (4.8)	7 (5.3)	3 (4.4)	10 (5.0)
Not Hispanic or Latino	118 (95.2)	61 (98.4)	179 (96.2)	113 (94.2)	61 (96.8)	174 (95.1)	91 (94.8)	48 (96.0)	139 (95.2)	126 (94.7)	65 (95.6)	191 (95.0)
Region[b]	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
US	6 (4.8)	2 (3.2)	8 (4.3)	8 (6.7)	3 (4.8)	11 (6.0)	6 (6.3)	3 (6.0)	9 (6.2)	8 (6.0)	4 (5.9	12 (6.0)
Non-US	118 (95.2)	60 (96.8)	178 (95.7)	112 (93.3)	60 (95.2)	172 (94.0)	90 (93.8)	47 (94.0)	137 (93.8)	125 (94.0)	64 (94.1)	189 (94.0)

BMI= Body mass index; SD = standard deviation; US -= United States
NOTE: The corresponding enrolled samples in the conversion phase, stabilization phase, double-blind maintenance phase and the trial period are included respectively. Age, weight, and BMI represent values at baseline of the conversion phase, stabilization phase, and double-blind maintenance phase, and the trial period respectively.
[a]Percentages are based on the number of male, female, or total enrolled sample in the corresponding phase or in the trial period.
[b]Region assigned by IWR.

Baseline disease severity:

Table 2.7.3.3.1.2-3 Baseline Disease Severity				
Parameter	**Conversion**	**Stabilization**	**Double-blind Maintenance**	
			Aripiprazole	**Placebo**
	N **Mean (SD)**	**N** **Mean (SD)**	**N** **Mean (SD)**	**N** **Mean (SD)**
Age of first diagnosis of schizophrenia	186 13.2 (2.1)	183 13.3 (2.2)	98 13.1 (2.3)	48 13.6 (2.0)
PANSS Total Score	185 86.9 (19.7)	183 78.9 (18.7)	98 65.5 (12.5)	48 62.9 (13.4)
Delusions (P1)	185 3.6 (1.5)	183 3.2 (1.4)	98 2.3 (1.1)	48 2.3 (1.1)
Conceptual Disorganization (P2)	185 3.4 (1.1)	183 3.2 (1.2)	98 2.5 (0.9)	48 2.5 (1.0)
Suspiciousness (P6)	185 3.6 (1.4)	183 3.2 (1.4)	98 2.5 (1.0)	48 2.5 (1.1)
Hallucinatory (P3)	185 3.1 (1.6)	183 2.6 (1.5)	98 1.7 (1.0)	48 2.0 (1.1)
Unusual Thought Content (G9)	185 3.2 (1.4)	183 2.8 (1.3)	98 2.2 (1.0)	48 2.3 (0.9)
CGI-S Score	186 4.2 (1.0)	183 3.9 (1.0)	98 3.2 (0.7)	48 3.0 (0.8)
CGI-I Score	N/A	N/A	98 2.4 (0.8)	48 2.5 (0.8)
CGAS Score	186 50.4 (13.0)	183 53.4 (12.8)	98 60.9 (11.6)	48 66.1 (12.4)

Note: The corresponding enrolled samples in the stabilization and double-blind maintenance phases are included respectively.
Note: Subjects randomized in the double-blind maintenance phase are included.
SD=standard deviation, PANSS=positive and negative syndrome scale, CGI-I=clinical global impressions of improvement, CGI-S=clinical global impressions of severity

Numbers analysed

A total of 244 subjects were screened for this trial. Over half the subjects screened for the trial came from the Russian Federation and India. A total of 201 subjects entered the trial and 146 subjects were randomized in the double-blind maintenance phase: 98 subjects in the aripiprazole group and 48 subjects in the placebo group. Of the 201 subjects who entered the trial, 56 (27.9%) subjects were between 13 and 14 years old and 145 (72.1%) subjects were at least 15 years old. Of 146 subjects who were randomized in the double-blind maintenance phase, 21 subjects completed the trial: 15 subjects in the aripiprazole group and 6 subjects in the placebo group. Of the 146 subjects randomized in the double-blind maintenance phase, 41 (28.8%) subjects were between the age of 13 and 14 years and 113 (77.4%) subjects were at least 15 years old. Female subjects and subjects aged 13 to 15 years were adequately represented in the subject population. The main reason for discontinuation from the trial was the sponsor discontinuing the trial (180 subjects [89.6%] total), which occurred after the 37th event of exacerbation of psychotic symptoms/impending relapse occurred. All subjects were analysed for safety and all subjects in the stabilization and double-blind maintenance phases were analysed for efficacy.

Outcomes and estimation

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.

Ancillary analyses

As only the younger subgroup (13-14 years) of the population of the trial was not already covered by the approved indication, a subgroup analysis by age is of interest. Despite the point estimates for the treatment effect are generally overlapping, the trial do not reach statistical significance for the main efficacy analysis in the younger subgroup.

In fact, for subjects receiving aripiprazole, relapse rates were comparable across age subgroups (20.69%, 13 - 14 years; 18.84%, 15 - 17 years), although the relapse rate with placebo was higher in the younger age subgroup. Point estimates for the hazard ratios (HRs) were also comparable between age subgroups (0.495, 13 - 14 years; 0.454, 15 - 17 years), but the absence of effect fell within the 95% confidence interval for the younger subgroup (0.151 to 1.628). The relapse rate with aripiprazole was lower than placebo overall and for both age subgroups; however, the log-rank test p-value for the treatment difference was statistically significant in favour of aripiprazole for the older subgroup (p = 0.0397), but not the younger subgroup (p = 0.2378).

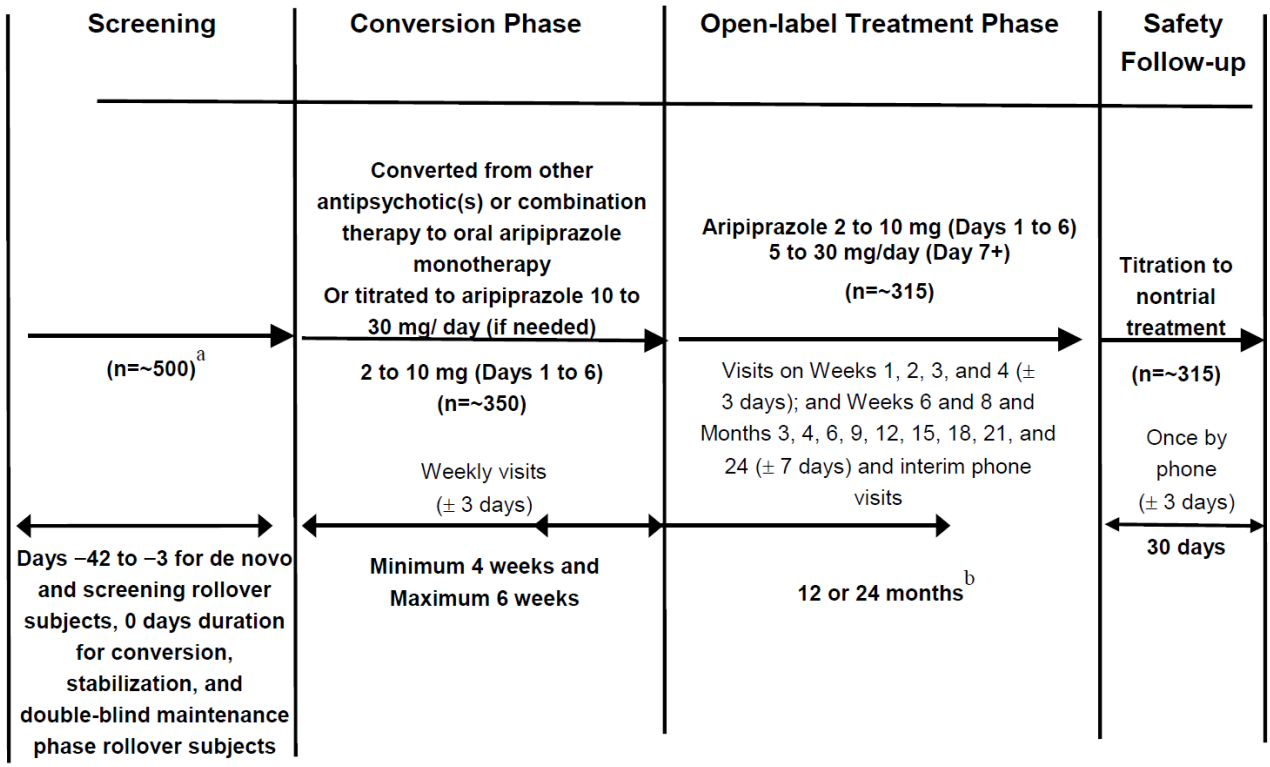
Study 31-09-267

A Long-term, Multicenter, Open-label Study to Evaluate the Safety and Tolerability of Flexible-dose Oral Aripiprazole (OPC-14597) as Maintenance Treatment in Adolescent Patients With Schizophrenia or Child and Adolescent Patients With Bipolar I Disorder, Manic or Mixed Episode With or Without Psychotic Features

Methods

Trial Design

This was an open-label trial of titrated aripiprazole to evaluate the safety and efficacy of aripiprazole tablets (10 to 30 mg/day) as maintenance treatment in adolescent subjects (13 to 17 years of age) with schizophrenia or child and adolescent subjects (10 to 17 years of age) with bipolar I disorder, manic or mixed episode, with or without psychotic features. The enrolled subject population of male and female subjects was comprised of child and adolescent subjects with a diagnosis or symptoms of schizophrenia or bipolar I disorder, manic or mixed episode with or without psychotic features, with a diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. This trial was conducted to further characterise 2 years of safety exposure with special focus on sexual maturation and growth, cognitive side effects, and the tolerability of aripiprazole 10 to 30 mg/day. Participants from the placebo-controlled Trial 31-09-266 were given the option to rollover to a one year openlabel follow up in the current trial on a compassionate basis. The data from these rollover subjects are shorter in duration and are not intended to be primarily used to satisfy the commitment to the PIP commitment nor should the safety data be combined for these 2 groups with such difference in the exposure time. This trial consists of a screening period, a conversion/titration phase, an open-label treatment phase, and a follow-up period. Individual participation for subjects who completed the trial ranged from a minimum of approximately 56 weeks to a maximum of 120 weeks. Length of participation varied depending on the screening duration (3 to 42 days for de novo subjects and 0 days for Trial 31-09-266 rollover subjects), the time required for conversion to aripiprazole monotherapy (0 to 6 weeks), the duration of open-label treatment (12 to 24 months ± 7 days), and 4-week post-trial follow up.



Schematic representation of the design for trial 31-09-267

Study Participants

The enrolled subject population of child and adolescent male and female subjects was planned to include approximately 500 de novo subjects either with schizophrenia or bipolar I disorder, manic or mixed episode and approximately 150 rollover subjects from Trial 31-09-266. The actual number of subjects enrolled was 524.

All de novo subjects were required to enter the screening period of the trial. De novo subjects could have two years exposure to aripiprazole while subjects who rolled over from the 31-09-266 trial could have one year exposure.

The 31-09-266 trial enrolled only subjects with schizophrenia. De novo subjects in the 31-09-267 were enrolled with a diagnosis of either schizophrenia or bipolar disorder. Due to the rollover population being all schizophrenic and the criteria for the 31-09-267 allowing for either diagnosis, the number of subjects with bipolar disorder enrolled was much smaller than subjects with schizophrenia in this trial.

Subjects who were screened and were not required to go through the conversion phase had to complete an open-label treatment phase baseline visit prior to their participation in the open-label treatment phase. Subjects from Trial 31-09-266 who were eligible for entry into this open-label trial, because they chose to continue treatment upon completion of Trial 31-09-266, bypassed screening and the conversion phase, but were required to reinitiate the fixed dose titration in the open-label treatment phase.

Treatments

Screening Period:

Screening was from Days −42 to −3. After the screening procedures were complete, eligible subjects underwent a washout of prohibited medications to be eligible to enter the conversion phase or the open-label treatment phase.

Conversion Phase (de novo subjects and subjects with schizophrenia who rolled over from the screening period or the conversion phase of Trial 31-09-266):

During the 4 to 6 weeks of the conversion phase, some of the de novo subjects were cross-titrated from their other antipsychotic(s) (if any) to oral trial aripiprazole target dose ranging from 10 to 30 mg/day. Subjects were required to receive a minimum dose of 10 mg daily to enter the open-label treatment phase from the conversion phase. Evaluations from the Week 6 (or end of the conversion phase) visit served as the baseline visit for the open-label treatment phase. Subjects who completed the screening period of Trial 31-09-266 rolled over into the conversion phase of Trial 31-09-267 and resumed dose titration in this trial at the week in the conversion phase that they had stopped in Trial 31-09-266.

Open-label Treatment Phase:

Subjects entered the open-label treatment phase directly after screening if they rolled over from the stabilization or double-blind maintenance phase of Trial 31-09-266 or if, as a de novo subject, they were already treated with oral aripiprazole monotherapy. Otherwise (ie, subjects naive to aripiprazole, or who were receiving more than 1 antipsychotic drug), subjects entered the open-label treatment phase after completing the conversion phase, and not directly after screening. The open-label treatment phase baseline trial procedures were performed prior to entering the open-label treatment phase. During the open-label treatment phase, subjects received trial aripiprazole within the approved dose range of 10 to 30 mg/day; nevertheless, the dose could have been lowered to 5 mg/day, if it was deemed necessary after Day 6, according to the investigator's clinical judgment. The length of treatment in the open-label treatment phase was determined by the following criteria:

- De novo subjects enrolled in the open-label treatment phase of this trial were eligible to receive up to 2 years (104 weeks) of open-label aripiprazole treatment.
- Rollover subjects enrolled in the open-label treatment phase of this trial were eligible to receive up to 1 year (52 weeks) of open-label aripiprazole treatment.

Safety Follow-up Phase:

A follow-up phone call to the subject/parent/guardian or legally acceptable representative, as applicable for local laws, occurred 30 +- 3 days after the End of Trial (Months 12 or 24)/ET visit to assess adverse events (AEs).

Objectives

The objective of the trial was to further characterize the long-term safety and tolerability of aripiprazole in adolescent subjects with schizophrenia and child and adolescent subjects with bipolar I disorder, manic or mixed episode, with or without psychotic features.

Outcomes/endpoints

Primary endpoint:

- frequency and severity of AEs, serious AEs (clinical and laboratory), and discontinuation from trial due to AEs.

Secondary safety endpoints included the following:

- Mean change from baseline and incidence of clinically significant abnormalities in clinical laboratory tests and urinalysis results (including fasting blood lipids, glucose, and insulin, serum prolactin, haemoglobin A1c, and creatinine phosphokinase), vital signs (supine and standing positions), and

ECG parameters. A central ECG service was utilized to review all ECGs to standardize interpretations for the safety analysis.

- Review of physical examination findings
- Mean change from baseline of z-scores for height and body weight, and mean changes of BMI and waist circumference
- Mean change from baseline on the AIMS, SAS, and BARS
- The frequency of symptom items for the clinician-administered NY-AACENT
- Baseline and post-baseline Tanner Staging
- Analysis of potential suicide events recorded on the C-SSRS
- Time to discontinuation due to AE

The secondary efficacy endpoints for subjects with schizophrenia included the following:

- Mean change from baseline in PANSS Total Score
- Mean change from baseline in PANSS Positive and Negative Subscale Scores
- Mean change from baseline in CGI-S Score
- Mean CGI-I Score at endpoint
- Mean change from baseline in CGAS

The secondary efficacy endpoints for subjects with bipolar manic or mixed episode included the following:

- Mean change from baseline in YMRS Score
- Mean change from baseline in CGI-BP Severity Score
- Mean CGI-BP Improvement Score at endpoint
- Mean change from baseline in GBI Score
- Mean change from baseline in ADHD-RS-IV Score
- Mean change from baseline in CGAS

The other efficacy endpoints included the following:

- Change from baseline for P-QLES-Q
- Mean change from baseline on the PANSS Cognitive Subscale Score
- Time to discontinuation for all reasons

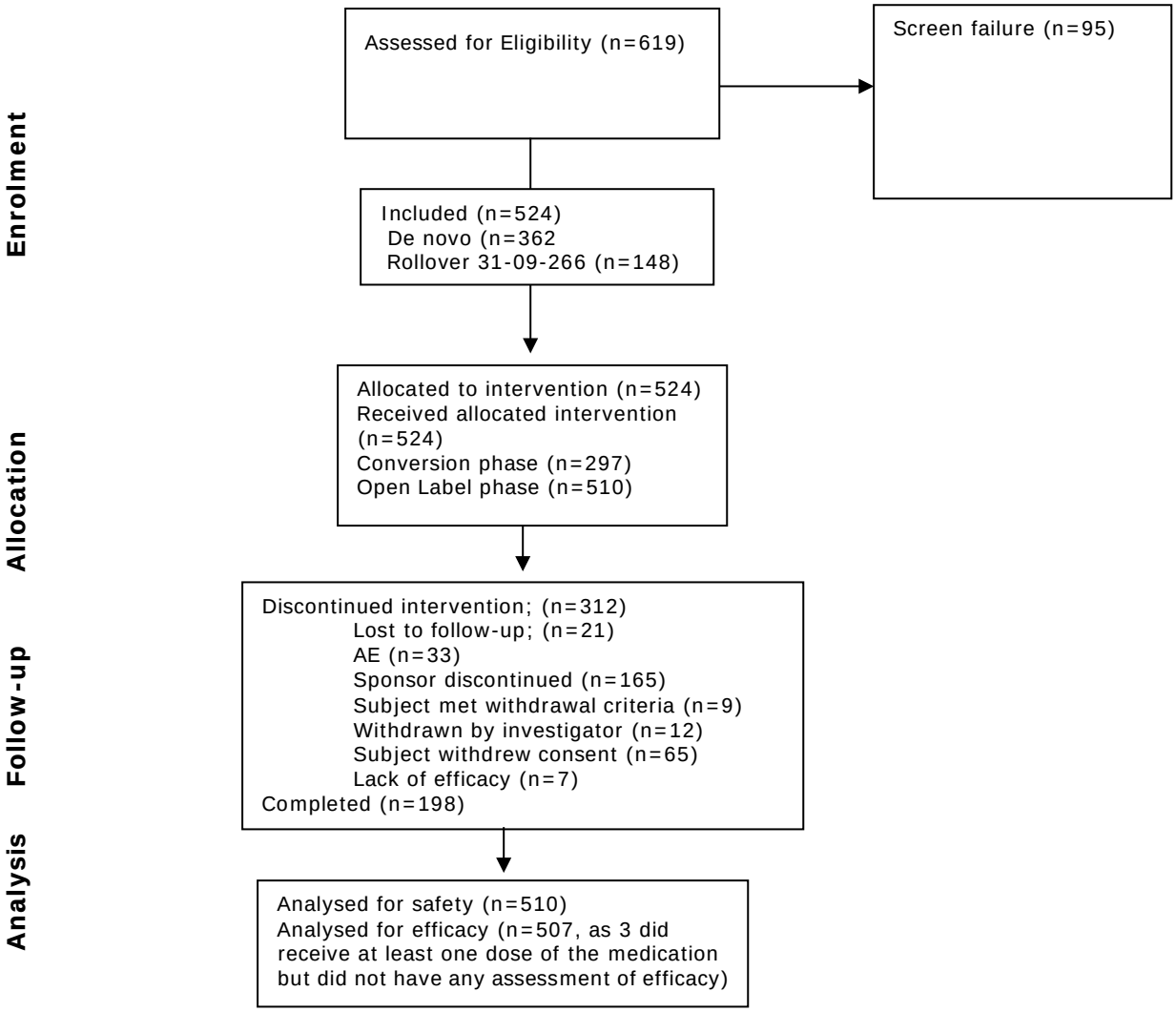
Statistical methods

For trial 31-09-267 no primary efficacy endpoints were defined. The secondary efficacy endpoints for the open-label treatment phase was the mean CGI-I Score for subjects with schizophrenia and CGI-BP Improvement Score for subjects with bipolar manic or mixed episode were summarized by descriptive statistics using the Open-label Treatment Phase Efficacy Sample. Descriptive statistics were provided for all other secondary efficacy endpoints in the form of mean change from baseline using the Open-label Treatment Phase Efficacy Sample. Descriptive statistics included mean, median, range, and SD, and were presented by enrolment source and target disease. The PANSS Total Score (range 30 to 120) is the sum of the rating scores for 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale

items. A missing value for any item(s) could have resulted in a missing PANSS Total Score. The PANSS Positive Subscale Score (range 7 to 49) is the sum of the rating scores for the 7 positive scale items from the PANSS scale. The PANSS Negative Subscale Score (range 7 to 49) is the sum of the rating scores for the 7 negative scale items from the PANSS scale. A missing value of any items in the PANSS positive or the negative items resulted in a missing subscale score. Higher scores in the PANSS assessments represent greater severity. The CGI-S and CGI-BP Severity Scores (range 1 to 7), as well as CGI-I and CGI-BP Improvement Scores (range 1 to 7) are single-item rating scores, with higher scores representing greater severity or less improvement. The CGAS Score (range 1 to 100) is a single-item score for rating a child's general level of functioning on a health-illness continuum, with higher scores representing better functioning. The YMRS Total Score (range 0 to 44) is the sum of the rating scores for 11 items for assessing the core symptoms of mania. A missing value for any YMRS assessment item(s) could have resulted in a missing YMRS Total Score. A higher YMRS Total Score represents greater severity. The GBI Total Score for mania (range 0 to 30) is the sum of scores for items 1 to 10 and the GBI Total Score for depression (range 0 to 30) is the sum of scores for items 11 to 20 in the GBI Parent/Guardian or Subject Version panel. Scores from the Parent/Guardian and Subject Versions were summarized separately. A missing value for any GBI assessment item(s) could have resulted in a missing GBI Total Score. High scores represent greater psychopathology. The ADHD-RS-IV Total Score (range 0 to 54) is the sum of rating scores for 18 items, with higher scores representing greater severity. A missing value for any ADHD-RS-IV assessment items could have resulted in a missing ADHD-RS-IV Total Score. Other endpoints included the change from baseline in P-QLES-Q Total and Overall Scores; change from baseline in the PANSS Cognitive Subscale Score, and time to discontinuation for all reasons other than sponsor terminating the trial. The change in the P-QLES-Q Total and Overall Scores and PANSS Cognitive Subscale Score data were listed for the conversion phase safety data and also summarized using descriptive statistics for the end of the open-label treatment phase and by visit for the open-label treatment phase safety data. Descriptive statistics included mean, median, range, and SD, and were presented by enrolment source and target disease. The Kaplan-Meier curve was plotted for time to discontinuation due to all causes other than sponsor terminating the trial for groups of subjects by enrolment source and target disease. The P-QLES-Q Total Score (range 14 to 70) is the sum of rating scores for items 1 to 14 and the P-QLES-Q Overall Score (range 1 to 5) are referred to as item 15 from the P-QLES-Q panel. A missing value for any one of the P-QLES-Q items 1 to 14 could have resulted in a missing P-QLES-Q Total Score. Higher scores in P-QLES-Q represent better performance of the assessed subjects. The PANSS Cognitive Subscale Score is the sum of rating scores for items G10, G11, G12, P2, N5, and N7 from the PANSS. A missing value for any one of the 6 items could have resulted in a missing PANSS Cognitive Subscale Score. The time to discontinuations due to all causes other than sponsor terminating the trial was measured from the date of entering the open-label treatment phase to the date of ET for discontinued subjects in the open-label treatment phase (i.e., time to discontinuation = date of discontinuation [or date of completion for completed subjects] – date of subject entering the open-label treatment phase + 1). If the subjects completed the trial or were discontinued due to the sponsor terminating the trial, they were censored at the time of completion or trial termination, respectively.

Results

Participant flow



Baseline data

A total of 524 subjects entered this trial: 362 subjects were de novo subjects and 148 subjects rolled over from Trial 31-09-266. The number of subjects with schizophrenia that entered this trial was 427 and the number of subjects with bipolar disorder was 97. A total of 158 de novo subjects participated in the trial for more than 728 days: 127 with schizophrenia and 31 with bipolar disorder. The de novo subset of the subject population is the primary dataset for the PIP commitment.

The majority of subjects who entered trial 31-09-267 were White (380 of 524 [72.5%] subjects) and not Hispanic or Latino (511 of 524 [97.5%] subjects). The next most frequently represented race was Asian (20.8%), followed by Black or African American, Other, and Native Hawaiian or Other Pacific Islander (5.0%, 1.5%, and 0.2%, respectively). A quarter of the subject was enrolled in EU member countries (Bulgaria,

Croatia, Hungary, Poland, and Romania). Overall, the mean (SD) age of subjects was 15.2 ± 1.6 years. The mean age of de novo subjects was 15.0 ± 1.6 (range: 10.0 to 17.0 years). The demographic characteristics of subjects who entered the conversion and open-label treatment period were similar. The mean (SD) age of first diagnosis of the target disease was 13.5 (2.3) years (range: 4 to 17) for the Open-label Treatment Phase Safety Sample. The mean (SD) PANSS Total Score at baseline was 68.2 (17.5) and the CGI-S Score was 3.4 (0.9) for de novo subjects with schizophrenia. For (de novo) bipolar subjects, the mean (SD) YMRS Total Score at baseline was 19.5 (8.8), and the CGI-BP Overall Bipolar Severity Score was 3.5 (1.2), and the CGI-BP Overall Bipolar Change Score was 2.3 (1.2).

Table 2.7.3.3.1.2-5 Demographics and Baseline Characteristics by Enrolment Source (Open-label Treatment Phase Safety Sample)

Parameter	Statistic	De Novo			Trial 31-09-266 Rollover			Total		
		Male N=210	Female N=152	Total N=362	Male N=97	Female N=51	Total N=148	Male N=307	Female N=203	Total N=510
Age (years)	Mean (SD)	15.0 (1.7)	15.0 (1.6)	15.0 (1.6)	15.7 (1.5)	15.8 (1.2)	15.8 (1.4)	15.2 (1.6)	15.2 (1.5)	15.2 (1.6)
	Range	10.0-17.0	10.0-17.0	10.0-17.0	13.0-18.0	13.0-18.0	13.0-18.0	10.0-18.0	10.0-18.0	10.0-18.0
Weight (kg)	Mean (SD)	64.5 (18.0)	57.3 (12.9)	61.5 (16.4)	64.9 (14.7)	59.3 (14.1)	63.0 (14.7)	64.6 (17.0)	57.8 (13.2)	61.9 (16.0)
	Range	35.0-116.6	27.0-112.0	27.0-116.6	39.8-100.0	36.0-101.6	36.0-101.6	35.0-116.6	27.0-112.0	27.0-116.6
Height (cm)	Mean (SD)	168.0 (11.2)	160.2 (7.2)	164.7 (10.5)	170.2 (10.2)	159.7 (8.1)	166.6 (10.8)	168.7 (11.0)	160.1 (7.4)	165.3 (10.6)
	Range	137.0-200.0	140.0-176.0	137.0-200.0	136.0-192.0	138.0-174.0	136.0-192.0	136.0-200.0	138.0-176.0	136.0-200.0
BMI (kg/m^2)	Mean (SD)	22.6 (4.9)	22.3 (4.5)[a]	22.5 (4.7)[b]	22.2 (3.8)	23.2 (5.1)	22.6 (4.3)	22.5 (4.6)	22.5 (4.6)[c]	22.5 (4.6)[d]
	Range	14.6-39.5	10.0-42.7	10.0-42.7	15.2-33.3	15.6-40.0	15.2-40.0	14.6-39.5	10.0-42.7	10.0-42.7
Race										
White	n (%)[e]	157 (74.8)	120 (78.9)	277 (76.5)	65 (67.0)	30 (58.8)	95 (64.2)	222 (72.3)	150 (73.9)	372 (72.9)
Black or African American	n (%)[e]	15 (7.1)	10 (6.6)	25 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	15 (4.9)	10 (4.9)	25 (4.9)
Asian	n (%)[e]	33 (15.7)	21 (13.8)	54 (14.9)	31 (32.0)	21 (41.2)	52 (35.1)	64 (20.8)	42 (20.7)	106 (20.8)
Native Hawaiian or Other Pacific Islander	n (%)[e]	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Other	n (%)[e]	4 (1.9)	1 (0.7)	5 (1.4)	1 (1.0)	0 (0.0)	1 (0.7)	5 (1.6)	1 (0.5)	6 (1.2)
Ethnicity										
Hispanic or Latino	n (%)[e]	3 (1.4)	3 (2.0)	6 (1.7)	4 (4.1)	1 (2.0)	5 (3.4)	7 (2.3)	4 (2.0)	11 (2.2)
Non-Hispanic or Latino	n (%)[e]	207 (98.6)	148 (97.4)	355 (98.1)	93 (95.9)	50 (98.0)	143 (96.6)	300 (97.7)	198 (97.5)	498 (97.6)
Unknown	n (%)[e]	0 (0.00)	1 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)

Age, weight, height, and BMI represent values at baseline of the open-label treatment phase. [a]N = 151. [b]N = 361. [c]N = 202. [d]N = 509. [e]Percentages are based on the number of male, female, or total subjects in the open-label treatment phase.

Table 2.7.3.3.1.2-6 Demographics and Baseline Characteristics by Target Disease (Open-label Treatment Phase Safety Sample)										
Parameter	**Statistic**	**Bipolar Disorder**			**Schizophrenia**			**Total**		
		Male N=52	**Female N=42**	**Total N=94**	**Male N=255**	**Female N=161**	**Total N=416**	**Male N=307**	**Female N=203**	**Total N=510**
Age (years)	Mean (SD)	13.7 (2.1)	14.1 (2.1)	13.9 (2.1)	15.5 (1.3)	15.5 (1.2)	15.5 (1.3)	15.2 (1.6)	15.2 (1.5)	15.2 (1.6)
	Range	10.0-17.0	10.0-17.0	10.0-17.0	13.0-18.0	13.0-18.0	13.0-18.0	10.0-18.0	10.0-18.0	10.0-18.0
Weight (kg)	Mean (SD)	63.9 (20.3)	57.4 (12.5)	61.0 (17.5)	64.8 (16.3)	57.9 (13.4)	62.1 (15.6)	64.6 (17.0)	57.8 (13.2)	61.9 (16.0)
	Range	35.7-106.1	38.5-93.9	35.7-106.1	35.0-116.6	27.0-112.0	27.0-116.6	35.0-116.6	27.0-112.0	27.0-116.6
Height (cm)	Mean (SD)	162.8 (13.4)	158.8 (7.3)	161.0 (11.2)	169.9 (10.0)	160.4 (7.4)	166.2 (10.2)	168.7 (11.0)	160.1 (7.4)	165.3 (10.6)
	Range	137.0-187.0	143.0-171.0	137.0-187.0	136.0-200.0	138.0-176.0	136.0-200.0	136.0-200.0	138.0-176.0	136.0-200.0
BMI (kg/m^2)	Mean (SD)	23.7 (5.7)	22.7 (4.4)	23.2 (5.1)	22.2 (4.3)	22.5 (4.7)[a]	22.3 (4.5)[b]	22.5 (4.6)	22.5 (4.6)[c]	22.5 (4.6)[d]
	Range	16.8-39.5	17.3-35.8	16.8-39.5	14.6-38.1	10.0-42.7	10.0-42.7	14.6-39.5	10.0-42.7	10.0-42.7
Race										
White	n (%)[e]	39 (75.0)	32 (76.2)	71 (75.5)	183 (71.8)	118 (73.3)	301 (72.4)	222 (72.3)	150 (73.9)	372 (72.9)
Black or African American	n (%)[e]	11 (21.2)	8 (19.0)	19 (20.2)	4 (1.6)	2 (1.2)	6 (1.4)	15 (4.9)	10 (4.9)	25 (4.9)
Asian	n (%)[e]	2 (3.8)	1 (2.4)	3 (3.2)	62 (24.3)	41 (25.5)	103 (24.8)	64 (20.8)	42 (20.7)	106 (20.8)
Native Hawaiian or Other Pacific Islander	n (%)[e]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.3)	0 (0.0)	1 (0.2)
Other	n (%)[e]	0 (0.0)	1 (2.4)	1 (1.1)	5 (2.0)	0 (0.0)	5 (1.2)	5 (1.6)	1 (0.5)	6 (1.2)
Ethnicity										
Hispanic or Latino	n (%)[e]	0 (0.0)	3 (7.1)	3 (3.2)	7 (2.7)	1 (0.6)	8 (1.9)	7 (2.3)	4 (2.0)	11 (2.2)
Non-Hispanic or Latino	n (%)[e]	52 (100.0)	38 (90.5)	90 (95.7)	248 (97.3)	160 (99.4)	408 (98.1)	300 (97.7)	198 (97.5)	498 (97.6)
Unknown	n (%)[e]	0 (0.0)	1 (2.4)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)

Age, weight, height, and BMI represent values at baseline of the open-label treatment phase. [a]N = 160. [b]N = 415. [c]N = 202. [d]N = 509. [e]Percentages are based on the number of male, female, or total subjects in the open-label treatment phase.

Table 2.7.3.3.1.2-7 Baseline Disease Severity							
Baseline Characteristic	**Statistic**	**Phase**		**Enrollment Source**		**Target Disease**	
		Conversion Phase N=297	**Open-label Treatment Phase N=510**	**De Novo N=362**	**Trial 31-09-266 Rollover N=148**	**Bipolar Disorder N=94**	**Schizophrenia N=416**
PANSS Total Score	N	253	415	267	148	-	415
	Mean (SD)	79.4 (18.6)	67.7 (17.8)	68.2 (17.5)	66.7 (18.3)	-	67.7 (17.8)
	Median	79.0	67.0	67.0	68.0	-	67.0
	Range	36, 130	30, 129	32, 129	30, 128	-	30, 129
Conceptual Disorganization (P2)	N	253	415	267	148	-	415
	Mean (SD)	3.0 (1.0)	2.7 (1.0)	2.6 (1.0)	2.7 (1.1)	-	2.7 (1.0)
	Median	3.0	3.0	3.0	3.0	-	3.0
	Range	1, 6	1, 6	1, 6	1, 6	-	1, 6
Suspiciousness (P6)	N	253	416	268	148	-	416
	Mean (SD)	3.2 (1.2)	2.6 (1.2)	2.5 (1.1)	2.6 (1.4)	-	2.6 (1.2)
	Median	3.0	3.0	3.0	3.0	-	3.0
	Range	1, 6	1, 6	1, 6	1, 6	-	1, 6
Hallucinatory (P3)	N	253	416	268	148	-	416
	Mean (SD)	2.7 (1.4)	2.0 (1.2)	2.1 (1.1)	1.9 (1.3)	-	2.0 (1.2)
	Median	3.0	2.0	2.0	1.0	-	2.0
	Range	1, 7	1, 6	1, 6	1, 6	-	1, 6
Unusual Thought Content (G9)	N	253	416	268	148	-	416
	Mean (SD)	3.0 (1.2)	2.4 (1.1)	2.4 (1.1)	2.3 (1.2)	-	2.4 (1.1)
	Median	3.0	2.0	2.0	2.0	-	2.0
	Range	1, 6	1, 6	1, 6	1, 6	-	1, 6
CGI-S Score	N	253	416	268	148	-	416
	Mean (SD)	4.0 (1.0)	3.4 (1.0)	3.4 (0.9)	3.3 (1.1)	-	3.4 (1.0)
	Median	4.0	3.0	3.0	3.0	-	3.0
	Range	1, 6	1, 6	1, 6	1, 6	-	1, 6
CGI-I Score	N	-	-	240	148	-	388
	Mean (SD)	-	-	2.9 (0.9)	3.6 (1.5)	-	3.2 (1.2)

Table 2.7.3.3.1.2-7 Baseline Disease Severity							
Baseline Characteristic	**Statistic**	**Phase**		**Enrollment Source**		**Target Disease**	
		Conversion Phase N=297	**Open-label Treatment Phase N=510**	**De Novo N=362**	**Trial 31-09-266 Rollover N=148**	**Bipolar Disorder N=94**	**Schizophrenia N=416**
Change Score	Mean (SD)	-	-	2.2 (1.1)	-	2.2 (1.1)	-
	Median	-	-	2.0	-	2.0	-
	Range	-	-	1, 4	-	1, 4	-
Age of First Diagnosis of Target Disease (Years)	N	297	510	-	-	94	416
	Mean (SD)	13.8 (2.2)	13.5 (2.3)	-	-	12.1 (3.0)	13.8 (2.1)
	Median	14.0	14.0	-	-	12.0	14.0
	Range	4, 17	4, 17	-	-	4, 17	4, 17

CGI-BP = Clinical Global Impression Scale - Bipolar Version; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; N = number; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; YMRS = Young Mania Rating Scale.
Note: Summarized for the Safety Sample of the corresponding phase, and all subjects who received at least 1 dose of trial medication during the trial for the total group.

Numbers analysed

A total of 524 subjects entered this trial (297 subjects in the conversion phase and 510 subjects in the open-label treatment phase). Overall, in the open-label treatment phase, 362 subjects were de novo subjects (280 subjects entered into the conversion phase) and 148 subjects rolled over from Trial 31-09-266 (3 subjects enrolled in the conversion phase prior to entering the open-label treatment phase). The number of subjects with schizophrenia that entered this trial at any phase was 427 and the number of subjects with bipolar disorder that entered this trial at any phase was 97. All of the subjects were analysed for safety (524 subjects) and 507 of 510 (99.4%) subjects in the open-label treatment phase were analysed for efficacy. A total of 158 de novo subjects participated in the trial for more than 728 days: 127 with schizophrenia and 31 with bipolar disorder. The de novo subset of the subject population is the primary dataset for the PIP commitment. Only 198 of 524 (37.8%) subjects completed the trial; 14 of 297 (4.7%) subjects discontinued during the conversion phase and 312 of 510 (61.2%) subjects discontinued from the open-label treatment phase. De novo and rollover subjects discontinued from the open-label treatment phase at rates of 185 of 362 (51.1%) subjects and 127 of 148 [85.8%] subjects, respectively. Subjects with bipolar disorder and subjects with schizophrenia discontinued from the open-label treatment phase at similar rates (59 of 94 [62.8%] subjects and 253 of 416 [60.8%] subjects, respectively). The most frequent reasons for subject discontinuation during any phase were sponsor discontinued trial (31.5%), subject withdrew consent (13.7%), and AE (6.9%). Most of the premature study discontinuations were from the open-label treatment phase rather than from the conversion phase. Of the most frequent reasons for subject discontinuation, de novo subjects and rollover subjects discontinued from the open-label treatment phase because the sponsor discontinued trial (16.3% and 71.6%, respectively). De novo and rollover subjects discontinued from the open-label treatment phase due to subject withdrew consent at rates of 14.4% and 8.8%, respectively, and due to AEs at rates of 7.7% and 3.4%, respectively. Of the most frequent reasons for subject discontinuation, schizophrenia subjects and bipolar subjects discontinued from the open-label treatment phase because sponsor discontinued trial at rates of 38.2% and 6.4%, respectively, and subjects with schizophrenia or bipolar disorder discontinued from the open-label treatment phase due to subject withdrew consent at rates of 11.8% and 17.0%, respectively). For all subjects, the most frequent reason for withdrawal of consent was the refusal of subjects who had just turned 18 years of age to sign the ICF. Only de novo subjects had up to 2 years of exposure, rollover subjects had up to 1 year of exposure. The de novo portion of the dataset is intended to address the PIP commitment, as described above; rollover subjects received open-label treatment after the participation of the placebo-controlled study in a compassionate use basis. The length of exposure is different between the de novo and rollover cohorts; therefore, the emphasis is on the de novo subject data.

Outcomes and estimation

Safety Results:

Overall, 349 of 510 (68.4%) subjects experienced a total of 1156 treatment-emergent adverse events (TEAEs): 278 of 362 (76.8%) de novo subjects and 71 of 148 (48.0%) rollover subjects. A total of 49 of 510 (9.6%) subjects experienced at least 1 serious TEAE: 42 of 362 (11.6%) de novo subjects and 7 of 148 (4.7%) rollover subjects. A total of 203 of 510 (39.8%) subjects had at least 1 TEAE that was considered by the investigator to be potentially causally related to the trial drug: 163 of 362 (45.0% de novo subjects and 40 of 148 (27.0%) rollover subjects. Overall, 32 of 510 (6.3%) subjects experienced at least 1 TEAE which led to discontinuation of the trial drug: 27 of 362 (7.5%) de novo subjects and 5 of 148 (3.4%) rollover subjects. The most frequently reported AEs of special interest among de novo subjects (9% to 13%) were EPS-, weight gain-, and sedation/somnolence-related TEAEs with suicideand orthostasis-related TEAEs reported less frequently (1% to 4%). Hepatic-, prolactin-, glucose-, and lipid parameter-related TEAEs were reported at a frequency of < 1%; no neuroleptic malignant syndrome (NMS)- or seizure-related TEAEs were reported. One death occurred during this trial. On Day 572 of the open-label treatment phase, Subject 621-5102 died of accidental acute heroin toxicity (Medical Dictionary for Regulatory Activities preferred term: toxicity to various agents). The fatal TEAE was considered severe, unrelated to trial medication, and was not suicide related.

Two pregnancies were reported during the trial and resulted in live births. The birth was uncomplicated for Subject 619-5402 and at the infant's 4-month check-up the child had reached all normal developmental milestones. The birth of Subject 617-5069's baby was via spontaneous vacuum-assisted vaginal delivery. The newborn had the umbilical cord wrapped 3 times around her leg, a caput succedaneum, a large middle digit on the right hand, bilateral wrist drop, upper extremity increased tone, and lower extremity decreased tone. There were no further updates to the condition of either mother or child. One potential Hy's law case was reported during this trial; this rollover subject had a concomitant TEAE of hepatitis A during the open-label treatment phase.

No clinically meaningful changes from baseline were observed in mean serum chemistry, hematology, urinalysis, or other laboratory test parameters in the open-label treatment phase.

Weight, BMI, and waist circumference increased steadily throughout the open-label treatment period. Based on the relatively stable weight and BMI z-scores data, the weight changes that occurred during the open-label treatment phase were consistent with growth and maturation of this pediatric population, aged 10 to 18 years.

The most frequently reported vital signs of potential clinical relevance during the open-label treatment period for de novo subjects included weight gain ≥ 7% in 168 of 361 (46.5%) subjects, increase in standing diastolic blood pressure ≥ 15 mmHg in 40 of 361 (11.1%) subjects, weight loss ≥ 7% in 39 of 361 (10.8%) subjects and increase in supine diastolic blood pressure ≥15 mmHg in 37 of 361 (10.2%) subjects). The frequency with which weight gain ≥7% occurred increased steadily throughout the trial.

No clinically meaningful changes from baseline were observed in the AIMS Movement Rating Score or the BARS Global Score in the open-label treatment phase. In general, the SAS Total Score using the LOCF dataset decreased throughout the open label treatment phase.

Overall, 275 of 362 (76.0%) de novo subjects had signs/symptoms (at least one occurrence) in the NY-AACENT; a majority of subjects had signs/symptoms of reasoning and problem solving (230 of 362 [63.5%] subjects), attention/vigilance (221 of 362 [61.0%] subjects), social cognition (215 of 362 [59.4%] subjects), and speed of processing (198 of 362 [54.7%] subjects).

There were no completed suicides in this trial. Overall during the open-label treatment phase, suicidality and suicidal ideation were reported on the C-SSRS for 8.3% of de novo subjects and 8.1% of de novo subjects,

respectively, with worsening and emergence of suicidal ideation reported for 6.9% of de novo subjects and 5.0% of de novo subjects, respectively.

Overall, 146 (40.3%) de novo subjects who were not already at Tanner Stage 5 (adult sexual maturity) progressed at least 1 stage from baseline as of the last assessment during the open-label treatment phase. A total of 132 de novo subjects (79 of 210 [37.6%] male subjects and 53 of 152 [34.9%] female subjects) were Tanner Stage 5 at baseline. Tanner Staging progression (ie, 1 to 3 stages from baseline) was similar for male and female de novo subjects during aripiprazole treatment (87 of 210 [41.4%] male subjects and 59 of 152 [38.8%] female subjects).

Efficacy Results:

Rapid symptom improvement in the PANSS Total Score, PANSS Positive Subscale Score, PANSS Negative Subscale Score, CGI-S Score, CGI-I Score, CGAS Score, CGI-BP Severity Score, CGI-BP Improvement Score, and PANSS Cognitive Subscale Score were observed for de novo subjects during the first 2 to 4 months of the open-label treatment phase of this trial. Subjects continued to improve throughout the rest of the trial, although at a slower rate than the first few months. Based on the GBI Total Score for Mania and Depression as well as the ADHD-RS-IV Total Score, bipolar subjects experienced a rapid improvement in symptoms reaching a maximum mean change from baseline between Weeks 3 and 8.

Mania symptoms rapidly improved for bipolar subjects based on the YMRS Total Score using the LOCF dataset over the first 8 weeks of the open-label treatment phase. After this initial improvement, the mean (SD) YMRS Total Score plateaued. Improvement of symptoms was also seen throughout the open-label treatment phase based on the P-QLES-Q Total and Overall Scores.

Overall, 147 of 510 (28.8%) subjects discontinued from the open-label treatment phase for reasons other than sponsor discontinued the trial (126 of 362 de novo subjects and 21 of 148 rollover subjects) with a median time to discontinuation of 768.0 days. A total of 73 of 268 (27.2%) de novo subjects with schizophrenia discontinued and 53 of 94 (56.4%) [de novo] subjects with bipolar disorder discontinued. There was no notable difference in discontinuation rate for de novo subjects based on subject age (36.4% for subjects < 15 years and 34.1% for subjects ≥15 years).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial 31-09-266

Title: A Long-Term Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Aripiprazole (OPC-14597) as Maintenance Treatment in Adolescent Patients with Schizophrenia.		
Study identifier	TRIAL 31-09-266	
Design	Randomised withdrawal trial	
	Duration of main phase:	52-week double blind, placebo-controlled maintenance phase
	Duration of Run-in phase:	Screening phase of 3 to 42 days 4 to 6 weeks conversion phase 7 weeks to 21 weeks stabilisation phase
	Duration of Extension phase:	Trial 31-09-267
Hypothesis	Superiority	
Treatments groups	Aripiprazole	10 to 30 mg; 52 Weeks, 98 pts
	Placebo	52 Weeks, 48 pts

Endpoints and definitions	Primary endpoint	*Time to exacerbation/ impending relapse*	Time to Exacerbation of Psychotic Symptoms/ Impending Relapse	
	Secondary endpoint	*% exacerbations*	Percentage of subjects meeting exacerbation of psychotic symptoms/ impending relapse criteria	
	Secondary endpoint	*% responders*	Percentage of responders in each treatment group, with response defined as meeting stability criteria, at last visit (not week 52)	
	Secondary endpoint	*% remissions*	Remission is defined as a score of $\leqslant$ 3, maintained for a period of 6 months on each of the following PANSS items: 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)	
	Secondary endpoint	*Discontinuation*	Time to discontinuation for any cause	
Database lock	Not available			
Results and Analysis				
Analysis population and time point description	Intent to treat 52 weeks			
Descriptive statistics and estimate variability	Treatment group		Aripiprazole 10 to 30 mg	Placebo
	Number of subjects		98	48
	Median to reach impending relapse		Not estimable as less than 50% of subjects reached the endpoint	Not estimable as less than 50% of subjects reached the endpoint
	Subjects meeting exacerbation of psychotic symptoms/ impending relapse criteria (%)		19.39	37.5
	Responders in each treatment group (%)		77.6	64.6
	Subjects achieving remission (%)		43.8	42.1
	Time to discontinuation for any cause (median)		Not estimable as less than 50% of subjects discontinued	271 days
Effect estimate per comparison	Primary endpoint – Time to exacerbation of psychotic symptoms/ Impending relapse		Comparison groups	Aripiprazole 10 to 30 mg vs. Placebo
			Odds ratio	0.461
			95% CI	0.242 to 0.879
			P-value (Cox proportional hazard model)	0.0161
	Secondary endpoint - Subjects meeting exacerbation of psychotic symptoms/ impending relapse criteria		Comparison groups	Aripiprazole 10 to 30 mg vs. Placebo
			P-value	0.0181
	Secondary endpoint – Responders		Comparison groups	Aripiprazole 10 to 30 mg vs. Placebo

		P-value	0.0962
	Secondary endpoint – Remitters	Comparison groups	Aripiprazole 10 to 30 mg vs. Placebo
		P-value	p = 0.9025
	Secondary endpoint – Discontinuation	Comparison groups	Aripiprazole 10 to 30 mg vs. Placebo
		P-value	0.0076

Table 2. Summary of Efficacy for trial 31-09-277

Title: A Long-term, Multicenter, Open-label Study to Evaluate the Safety and Tolerability of Flexible-dose Oral Aripiprazole (OPC-14597) as Maintenance Treatment in Adolescent Patients With Schizophrenia or Child and Adolescent Patients With Bipolar I Disorder, Manic or Mixed Episode With or Without Psychotic Features					
Study identifier	TRIAL 31-09-267				
Design	Safety study enrolling naïve patients going through a conversion to aripiprazole plus titration and roll over patients from 31-09-266 going directly to open label phase				
	Duration of main OL phase Duration of screening phase Duration of Conversion phase Duration of follow up		12 or 24 months 39 days (naïve patients) 4 to 6 weeks 30 days		
Hypothesis	Exploratory safety study				
Treatments groups	Aripiprazole flexible dose		10 to 30 mg; up to 24 months, 524 pts		
Endpoints and definitions	Primary endpoint	*AEs*	Frequency and severity of AEs, serious AEs (clinical and laboratory), and discontinuation from trial due to AEs (see Clinical Safety)		
Database lock	Not available				
Results and Analysis					
Analysis population and time point description	Modified ITT enrolled subjects analysis of de novo patients LOCF				
Descriptive statistics and estimate variability	Subgroup		10 to 14 years	15 to 17 years	Total
	Number of subjects		112	250	362
	Patients with AEs		85	193	278
	AEs		451	826	1277
	TEAEs		364	641	1005
	Patients with Serious TEAs		13	29	42
	Patients with Severe TEAs		10	20	30
	Patients who discontinued due to AEs		5	22	27
	Deaths		0	1	1

3.1.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study 31-09-266 was a placebo controlled paediatric study in schizophrenia, with most centres outside EU. It is acknowledged that ethical issues prevent in some countries, particularly in EU, to conduct a trial on schizophrenic patients with a placebo arm. Thereby studied population came mostly from non EU countries, where clinical practice in paediatric psychiatry and access to psychiatric support and medication may be different from most EU. Given that a large number of patients studied were indeed from Russian and Asian centres, the applicant was requested to show that these patients (particularly those who are 13 and 14 year old) are representative of the EU population. In its responses, the MAH stressed out that 12% of patients enrolled in study 266 were from EU (albeit from a single country – Romania). A comparison between EU countries and the other world regions did not exhibit relevant differences. This comparison however is between Eastern Countries and the rest of the world, and not between non Eastern EU countries vs Eastern countries. The CHMP was of the opinion that the same doubt subsisted as in particular in these countries, full access to atypical antipsychotics are not universal, jeopardizing external validity.

The study did not include an active comparator arm, and most of the patients did not reach end of study due to the decision of sponsor rather than impending relapse. Furthermore patient time "in trial" was considered short for the primary endpoint (mean days on ARI: 184; mean days on placebo: 158).

Efficacy data and additional analyses

The high (42.1%) proportion of remitters in the placebo arm poses into question the diagnosis of schizophrenia in the patients studied, as this rests primarily on the course of the disease (episodic, often after prodromal phase, with incomplete recovery between episodes) and hence the generalisation of the results to the target population. On this point the Applicant, upon request, clarified that the remitters rate is dependent on the actual time on study, and it is not, due to the termination of the study due to decision of sponsor, a 1-year remitters rate.

However, the lack of precision of the estimation of the hazard ratio for the patients aged 13 to 14 (whose 95% confidence interval ranges from 0.151 to 1.628) – probably also due to the small number – does not allow to draw a conclusion on the presence of a treatment effect

3.1.3. Conclusions on the clinical efficacy

The CHMP considered that the data provided could not support the level of efficacy required for an extension of indication for the age range 13-14 years of age.

3.2. Clinical safety

Introduction

Data from two clinical trials with aripiprazole for the treatment of schizophrenia or bipolar I disorder, manic or mixed episode with or without psychotic features in child and adolescent subjects is presented fr discussion. The safety profile observed for aripiprazole in paediatric schizophrenia and bipolar mania subjects has similitude with the known product safety profile in adults, as observed from both clinical trials and post-marketing reports. No new types of adverse events (AEs) were observed in the paediatric population than were reported in the adult population. However, variations for certain AEs were observed between the adult and paediatric populations. For adolescent subjects with schizophrenia, the recommended target dose of Abilify is 10 mg/day. Aripiprazole was studied in the present trials at daily doses of 10 to 30 mg in adolescent subjects (13 to 17 years of age) with schizophrenia and child and adolescent subjects (10 to 17 years of age) with bipolar I disorder, manic or mixed episode with or without psychotic features.

Study 31-09-266

Patient exposure

During the stabilization 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. 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. The minimum number of days of aripiprazole exposure in the double-blind maintenance phase was 6 days and maximum was 371 days.

Table: patient exposure by phase

Phase	Study Week	Double-blind Maintenance Phase Treatment					
		Aripiprazole N=98		Placebo N=48		Total N=146	
		Average Daily Dose (mg)		Average Daily Dose (mg)		Average Daily Dose (mg)	
		N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)
Stabilization	Week 1	98 (100.0)	16.8 (6.2)	48 (100.0)	15.3 (5.4)	146 (100.0)	16.3 (6.0)
	Week 2	98 (100.0)	17.5 (6.1)	48 (100.0)	16.2 (5.6)	146 (100.0)	17.1 (6.0)
	Week 4	98 (100.0)	18.2 (6.2)	48 (100.0)	17.4 (6.0)	146 (100.0)	18.0 (6.1)
	Week 6	98 (100.0)	18.5 (6.3)	48 (100.0)	17.5 (6.1)	146 (100.0)	18.2 (6.2)
	Week 8	79 (80.6)	19.2 (6.7)	36 (75.0)	18.0 (6.4)	115 (78.8)	18.8 (6.6)
	Week 10	60 (61.2)	19.9 (6.8)	23 (47.9)	18.9 (6.1)	83 (56.8)	19.6 (6.6)
	Week 12	50 (51.0)	19.5 (7.1)	18 (37.5)	18.1 (6.2)	68 (46.6)	19.1 (6.9)
	Week 14	43 (43.9)	19.8 (7.2)	17 (35.4)	18.2 (6.4)	60 (41.1)	19.3 (6.9)
	Week 16	36 (36.7)	19.8 (7.3)	15 (31.3)	17.6 (5.9)	5 (34.9)	19.2 (6.9)
	Week 18	29 (29.6)	19.5 (6.9)	13 (27.1)	16.5 (5.2)	42 (28.8)	18.6 (6.5)
	Week 20	15 (15.3)	18.7 (5.9)	8 (16.7)	16.3 (5.2)	23 (15.8)	17.9(5.6)
	Week 21	10 (10.2)	18.1 (4.8)	5 (10.4)	14.0 (4.2)	15 (10.3)	16.7 (4.9)
	>Week 21	3 (3.1)	16.7 (2.9)	3 (6.3)	13.3 (5.8)	6 (4.1)	15.0 (4.5)
	Overall	98 (100.0)	18.4 (6.1)	48 (100.0)	17.1 (5.9)	146 (100.0)	18.0 (6.1)
Double-blind Maintenance	≤ Week 1	98 (100.0)	19.3 (6.7)	48 (100.0)	17.7 (6.6)	146 (100.0)	18.8 (6.7)
	Week 2	96 (98.0)	19.4 (6.7)	47 (97.9)	17.6 (6.7)	143 (97.9)	18.8 (6.7)
	Week 3	94 (95.9)	19.3 (6.6)	46 (95.8)	17.7 (6.7)	140 (95.9)	18.8 (6.6)
	Week 4	93 (94.9)	19.1 (6.9)	43 (89.6)	17.7 (6.8)	136 (93.2)	18.6 (6.9)
	Week 5	89 (90.8)	19.2 (6.8)	41 (85.4)	17.1 (6.3)	130 (89.0)	18.5 (6.7)
	Week 6	89 (90.8)	19.2 (6.7)	41 (85.4)	17.1 (6.3)	130 (89.0)	18.5 (6.6)
	Week 8	82 (83.7)	19.7 (6.7)	37 (77.1)	17.4 (6.4)	119 (81.5)	19.0 (6.7)
	Week 10	76 (77.6)	19.4 (6.5)	32 (66.7)	16.4 (5.9)	108 (74.0)	18.5 (6.5)
	Week 12	71 (72.4)	19.6 (6.7)	31 (64.6)	16.0 (5.4)	102 (69.9)	18.5 (6.5)
	Week 14	69 (70.4)	19.5 (6.8)	27 (56.3)	16.3 (5.1)	96 (65.8)	18.6 (6.5)
	Week 16	65 (66.3)	19.1 (6.7)	24 (50.0)	16.9 (5.1)	89 (61.0)	18.5 (6.4)
	Week 18	61 (62.2)	18.9 (6.8)	23 (47.9)	17.2 (5.0)	84 (57.5)	18.4 (6.3)
	Week 20	57 (58.2)	18.7 (6.6)	23 (47.9)	17.2 (5.0)	80 (54.8)	18.3 (6.2)
	Week 22	55 (56.1)	19.0 (6.7)	21 (43.8)	16.9 (5.1)	76 (52.1)	18.4 (6.3)
	Week 24	52 (53.1)	18.8 (6.7)	19 (39.6)	16.6 (5.3)	71 (48.6)	18.2 (6.4)
Double-blind Maintenance	Week 26	48 (49.0)	18.8 (6.5)	19 (39.6)	16.6 (5.3)	67 (45.9)	18.2 (6.2)
	Week 28	43 (43.9)	19.0 (6.9)	17 (35.4)	17.1 (5.3)	60 (41.1)	18.4 (6.5)

Phase	Study Week	Double-blind Maintenance Phase Treatment					
		Aripiprazole N=98		Placebo N=48		Total N=146	
		Average Daily Dose (mg)		Average Daily Dose (mg)		Average Daily Dose (mg)	
		N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)
	Week 30	40 (40.8)	19.1 (6.9)	16 (33.3)	16.6 (5.1)	56 (38.4)	18.4 (6.5)
	Week 32	39 (39.8)	19.2 (6.9)	16 (33.3)	16.6 (5.1)	55 (37.7)	18.5 (6.5)
	Week 34	38 (38.8)	19.3 (7.0)	15 (31.3)	16.7 (5.2)	53 (36.3)	18.6 (6.6)
	Week 36	36 (36.7)	19.4 (7.1)	15 (31.3)	16.7 (5.2)	51 (34.9)	18.6 (6.7)
	Week 38	33 (33.7)	18.8 (7.0)	13 (27.1)	16.5 (5.5)	46 (31.5)	18.2 (6.6)
	Week 40	29 (29.6)	18.3 (6.7)	11 (22.9)	15.5 (5.2)	40 (27.4)	17.5 (6.4)
	Week 42	27 (27.6)	18.0 (6.8)	10 (20.8)	15.5 (5.5)	37 (25.3)	17.3 (6.5)
	Week 44	21 (21.4)	16.7 (5.8)	9 (18.8)	15.6 (5.8)	30 (20.5)	16.3 (5.7)
	Week 46	18 (18.4)	16.6 (5.7)	8 (16.7)	15.5 (6.3)	26 (17.8)	16.3 (5.8)
	Week 48	18 (18.4)	16.6 (5.7)	8 (16.7)	15.6 (6.2)	26 (17.8)	16.3 (5.8)
	Week 50	17 (17.3)	16.6 (5.8)	7 (14.6)	15.7 (6.7)	24 (16.4)	16.4 (5.9)
	Week 52	15 (15.3)	17.0 (6.2)	6 (12.5)	16.7 (6.8)	21 (14.4)	16.9 (6.2)
	>Week 52	9 (9.2)	17.2 (7.1)	3 (6.3)	16.7 (7.6)	12 (8.2)	17.1 (6.9)
	Overall	98 (100.0)	19.2 (6.7)	48 (100.0)	17.7 (6.6)	146 (100.0)	18.7 (6.7)

Note: Percentages are based on the number of subjects randomized.
In the double-blind maintenance phase, the extent of exposure to placebo was summarized for the placebo group.

A total of 244 subjects were screened for this trial. Over half the subjects screened for the trial came from the Russian Federation and India. A total of 201 subjects entered the trial and 146 subjects were randomized in the double-blind maintenance phase: 98 subjects in the aripiprazole group and 48 subjects in the placebo group. Of the 201 subjects who entered the trial, 56 (27.9%) subjects were between 13 and 14 years old and 145 (72.1%) subjects were at least 15 years old. Of 146 subjects who were randomized in the double-blind maintenance phase, 21 subjects completed the trial: 15 subjects in the aripiprazole group and 6 subjects in the placebo group. Of the 146 subjects randomized in the double-blind maintenance phase, 41 (28.8%) subjects were between the age of 13 and 14 years and 113 (77.4%) subjects were at least 15 years old. Female subjects and subjects aged 13 to 15 years were adequately represented in the subject population. The main reason for discontinuation from the trial was the sponsor discontinuing the trial (180 subjects [89.6%] total), which occurred after the 37th event of exacerbation of psychotic symptoms/impending relapse occurred. All subjects were analysed for safety and all subjects in the stabilization and double-blind maintenance phases were analysed for efficacy.

Table: subject disposition

Subjects	Conversion	Stabilization	Double-blind Maintenance Aripiprazole	Double-blind Maintenance Placebo	Total
	N (%)[a]	N (%)[a]	N (%)[b]	N (%)[b]	N (%)[b]
Screened					244
Screen Failure					43
Entered	186 (100.0)	183 (100.0)	98 (100.0)	48 (100.0)	201 (100.0)
Entered Next Phase	168 (90.3)	146 (79.8)	N/A	N/A	N/A
Randomized	N/A	N/A	98 (100.0)	48 (100.0)	146 (100.0)
Completed[c]	N/A	N/A	15 (15.3)	6 (12.5)	21 (10.4)
Discontinued	18 (9.7)	37 (20.2)	83 (84.7)	42 (87.5)	180-(89.6)
Lost to follow up	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Sponsor discontinued trial	4 (2.2)	16 (8.7)	58 (59.2)	19 (39.6)	97 (48.3)
Met withdraw criteria	1 (0.5)	7 (3.8)	0 (0.0)	0 (0.0)	8 (4.0)
Withdrawn by investigator	2 (1.1)	3 (1.6)	1 (1.0)	0 (0.0)	6 (3.0)
Subject withdrew consent	7 (3.8)	5 (2.7)	4 (4.1)	4 (8.3)	20 (10.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE without lack of efficacy (Conversion or Stabilization) or impending relapse (Double-blind Maintenance)	3 (1.6)	6 (3.3)	1 (1.0)	1 (2.1)	11 (5.5)
Lack of efficacy (Conversion or Stabilization) or impending relapse with AE (Double-blind Maintenance)	0 (0.0)	0 (0.0)	19 (19.4)	18 (37.5)	37 (18.40)
Lack of efficacy (Conversion or Stabilization) or impending relapse without AE (Double-blind Maintenance)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Analysed for Safety[d]	186 (100.0)	183 (100.0)	98 (100.0)	48 (100.0)	N/A
Analysed for Efficacy[e]	N/A	183 (100.0)	98 (100.0)	48 (100.0)	N/A

AE = Adverse Event

aNote: Percentages are based on the number of enrolled subjects in the corresponding phase.

bNote: Percentages are based on the number of subjects randomized in the double-blind maintenance phase.

cSubjects completed the double-blind maintenance phase Week 52 visit.

dSubjects receiving at least one dose of study medication in the corresponding phase are included in the safety analysis.

eSubjects evaluated for at least one efficacy endpoint in the corresponding phase are included in the efficacy analysis.

Adverse events

In the stabilization phase of trial 31-09-266, a total of 183 (100.0%) subjects were treated with aripiprazole oral tablets. A total of 109 (59.6%) subjects reported TEAEs. Four (2.2%) subjects reported serious TEAEs and 4 (2.2%) subjects reported TEAEs that were considered severe in severity. A total of 7 (3.8%) subjects discontinued trial medication due to AEs. A total of 146 subjects were randomized in the double-blind maintenance phase (98 subjects in the aripiprazole group and 48 subjects in the placebo group). 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 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%]). A total of 20 subjects (20.4%) in the aripiprazole group and 19 subjects (39.6%) in the placebo group discontinued trial medication due to AEs.

Table: summary of AEs

	Double-blind Maintenance Phase Treatment			
	Aripiprazole		Placebo	
	N	(%)[a]	N	(%)[a]
Number of:				
Subjects treated with aripiprazole oral tablets	98	(100.0)	48	(100.0)
Subject days of aripiprazole oral tablets exposure	18042		7584	
Subjects with AEs	64	(65.3)	33	(68.8)
Adverse events	154		87	
Subjects with TEAEs	64	(65.3)	33	(68.8)
Treatment-emergent adverse events[b]	140		79	
Subjects with serious TEAEs	3	(3.1)	6	(12.5)
Subjects with severe TEAEs	2	(2.0)	5	(10.4)
Subjects discontinued trial medication due to AE	20	(20.4)	19	(39.6)

[a]Percentages are based on the number of treated randomized subjects.
[b]A TEAE is defined as an AE that started after start of IMP treatment; or if the event was continuous from baseline and was serious, study drug related, or resulted in death, discontinuation, interruption or reduction of IMP.

Common Adverse Events

A similar percentage of subjects in the aripiprazole and placebo treatment groups in trial 31-09-266 reported TEAEs in the double-blind maintenance phase. A larger percentage of subjects discontinued trial medication due to AEs in the placebo group than in the aripiprazole group (39.6% of placebo subjects compared to 20.4% of aripiprazole subjects). A total of 45 (45.9%) subjects reported TEAEs considered by the investigator as potentially causally related to IMP in the aripiprazole group compared to 29 (60.4%) subjects in the placebo group.

TEAEs

In trial 31-09-266, a total of 64 (65.3%) TEAEs were reported in the aripiprazole group vs 33 (68.8%) TEAEs reported in the placebo group. Schizophrenia was the most frequently reported TEAE by the aripiprazole group and the placebo group, 10 subjects (10.2%) and 13 subjects (27.1%), respectively. Insomnia (considered a symptom of worsening schizophrenia) was reported by more placebo subjects than aripiprazole subjects, 9 subjects (18.8%) and 5 subjects (5.1%), respectively. Psychotic disorder was reported as a TEAE by 9 subjects (9.2%) in the aripiprazole group and in 5 subjects (10.4%) in the placebo group. Weight increased was reported by 8 subjects (8.2%) in the aripiprazole group and by 5 subjects (10.5%) in the placebo group. The aripiprazole group reported more TEAEs of nasopharyngitis (7 subjects [7.1%]) compared to the placebo group (1 subject [2.1%]). Most TEAEs were mild or moderate in severity.

Table: Incidence of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term in ⩾ 5% (Double-blind Maintenance Phase Safety Sample)

MedDRA System Organ Class and Preferred Term	Aripiprazole N=98		Placebo N= 48	
	n	(%)	n	(%)
Gastrointestinal Disorders				
Nausea	1	(1.0)	3	(6.3)
Infections and Infestations				
Nasopharyngitis	7	(7.1)	1	(2.1)
Investigations				
Weight Increased	8	(8.2)	5	(10.4)
Nervous System Disorders				
Akathisia	3	(3.1)	3	(6.3)
Headache	6	(6.1)	4	(8.3)
Tremor	4	(4.1)	4	(8.3)
Psychiatric Disorders				
Insomnia	5	(5.1)	9	(18.8)
Psychotic Disorder	9	(9.2)	5	(10.4)
Schizophrenia	10	(10.2)	13	(27.1)
Total	64	(65.3)	33	(65.8)

Note: A treatment-emergent adverse event is defined as an adverse event that started after start of trial drug treatment; or if the event was continuous from baseline and was serious, study drug related, or resulted in death, discontinuation, interruption or reduction of study therapy.
Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.
The double-blind maintenance phase AEs represent subjects who were previously stabilized to aripiprazole during earlier phases.
Schizophrenia and psychotic disorder terms represented impending relapses.

Serious adverse event / deaths / other significant events

Deaths

There were no deaths in this trial.

Other SAEs 31-09-266

The number of serious TEAEs was higher in the placebo group, 6 subjects (12.5%) vs the aripiprazole group 3 subjects (3.1%). The placebo group had 5 (10.4%) subjects with serious TEAEs of schizophrenia compared to the aripiprazole group, who had 1 (1.0%) subject with a serious TEAE of schizophrenia. Of the 5 serious TEAEs of schizophrenia in the placebo group, 3 events were considered moderate in severity and 2 events were considered severe in severity. The serious TEAE of schizophrenia in the aripiprazole group was considered mild in severity. The aripiprazole group had 2 (2.0%) subjects with serious TEAEs of psychotic disorder compared to the placebo group who had 1 (2.1%) subject with a serious TEAE of psychotic disorder. The 2 serious TEAEs of psychotic disorder in the aripiprazole group were considered moderate in severity while the 1 serious TEAE of psychotic disorder in the placebo group was considered to be moderate in severity.

MedDRA System Organ Class and Preferred Term	Aripiprazole N=98		Placebo N=48	
	n	(%)	n	(%)
Psychiatric Disorders				
Psychotic Disorder	2	(2.0)	1	(2.1)
Schizophrenia	1	(1.0)	5	(10.4)
Total[a]	3	(3.1)	6	(12.5)

Note: A treatment-emergent adverse event is defined as an adverse event that started after start of study drug treatment; or if the event was continuous from baseline and was serious, study drug related, or resulted in death, discontinuation, interruption or reduction of study therapy.
Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.
[a]Subjects with adverse events in multiple system organ classes were counted only once towards the total.

Other Significant Adverse Events

There were 11 defined adverse events of special interest (AESI) for trial 31-09-266. These included AEs relating to EPS, neuroleptic malignant syndrome (NMS), seizures, orthostasis, suicide, sedation/somnolence, glucose levels, lipid parameters, weight gain, prolactin levels, and hepatic functioning. No adverse events of special interest relating to EPS, NMS, seizure, orthostasis events, suicide, sedation and somnolence, glucose, lipid parameters, weight gain, prolactin and hepatic events in the Double-blind Maintenance Phase occurred more frequently in the aripiprazole group compared to the placebo group due to the previous stabilization of subjects on aripiprazole in the conversion and stabilization phases. The most common AESI 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 AESIs relating to NMS, seizures, orthostasis, glucose levels, or prolactin.

Vital Signs

The most frequently reported vital signs of potential clinical relevance during the open-label treatment period for de novo subjects included weight gain $\geqslant$ 7% in 168 of 361 (46.5%) subjects, increase in standing diastolic blood pressure $\geqslant$ 15 mmHg in 40 of 361 (11.1%) subjects, weight loss $\geqslant$ 7% in 39 of 361 (10.8%) subjects and increase in supine diastolic blood pressure $\geqslant$ 15 mmHg in 37 of 361 (10.2%) subjects. The frequency with which weight gain $\geqslant$ 7% occurred increased steadily throughout the trial. The most frequently reported vital sign-related TEAEs during the open-label treatment period for de novo subjects were increased weight in 32 of 362 (8.8%) subjects and pyrexia in 12 of 362 (3.3%) subjects. Weight and BMI z-scores deviated little from the mean of the age and gender reference population, and changed little from baseline. Based on the relatively stable weight and BMI z-scores, the weight changes that occurred during the open-label treatment phase were consistent with growth and maturation of this paediatric population, aged 10 to 18 years.

Electrocardiogram: During the open-label treatment phase, the RR interval had a steady increase from baseline, with a mean (SD) change from baseline of 31.7 (135.6) msec at Month 24. The most frequently reported ECG measurements of potential clinical relevance in de novo subjects were premature supraventricular beat (11 of 361 [3.0%] subjects), bradycardia (9 of 361 [2.5%] subjects), sinus bradycardia (9 of 361 [2.5%] subjects), right bundle branch block (6 of 361 [1.7%] subjects), and premature ventricular beat (6 of 361 [1.7%] subjects). The most frequently reported TEAEs related to ECG parameters in de novo subjects included conduction disorder (2 of 362 [0.6%] subjects) and prolonged QT electrocardiogram (2 of 362 [0.6%] subjects).

Simpson-Angus Scale

SAS Total Score using the LOCF dataset decreased throughout the open-label treatment phase in trial 31-09-266. The mean (SD) change from baseline for de novo subjects at Month 12 was −0.46 (1.72) and at Month 24 was −0.53 (1.81). Similar data were observed using the OC dataset.

New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment

275 of 362 (76.0%) de novo subjects had any signs/symptoms (at least one occurrence) in the NY-AACENT; a majority of subjects had signs/symptoms of reasoning and problem solving (230 of 362 [63.5%] subjects), attention/vigilance (221 of 362 [61.0%] subjects), social cognition (215 of 362 [59.4%] subjects), and speed of processing (198 of 362 [54.7%] subjects). Function-impaired signs/symptoms in the NY-AACENT were reported for 206 of 362 (56.9%) de novo subjects. The most frequently reported function-impaired signs/symptoms included reasoning and problem solving (168 of 362 [46.4%] subjects), social cognition (154 of 362 [42.5%] subjects), and attention/vigilance (150 of 362 [41.4%] subjects). Most of the NY-AACENT signs/symptoms, including function-impaired signs/symptoms, were mild to moderate in severity. Extreme symptoms were reported for social cognition (4 of 510 [0.8%] de novo subjects), reasoning and problem solving (2 of 510 [0.4%] de novo subjects), and attention/vigilance (1 of 510 [0.2%] de novo subjects). Trial medication-related, mild and moderate, function-impaired signs/symptoms in the NY-AACENT Total Score were reported for 1 to 3 subjects at each time point. No subjects had mean changes from baseline in the NY-AACENT Total Score of trial medication-related, function-impaired signs/symptoms that were considered severe or extreme.

Positive and Negative Syndrome Scale Cognitive Subscale Score

Rapid symptom improvements for subjects with schizophrenia in PANSS Cognitive Subscale Score using the LOCF dataset were observed for de novo subjects during the first 3 to 4 months of the open-label treatment phase, followed by gradual improvement for the duration of the open-label treatment phase. De novo subjects had mean (SD) change from baseline of −2.07 (4.01) at Month 12 and −2.51 (4.01) at Month 24. Similar results were observed with the OC dataset.

Columbia-Suicide Severity Rating Scale

There were no completed suicides in trial 31-09-266. During the open-label treatment phase, suicidality was reported on the C-SSRS by 30 of 360 (8.3%) de novo subjects and suicidal ideation was reported by 29 of 360 (8.1%) de novo subjects. Worsening and emergence of suicidal ideation was reported by 25 of 360 (6.9%) de novo subjects and 18 of 360 (5.0%) de novo subjects, respectively

Tanner Staging

Of the 362 de novo subjects with baseline and post-baseline Tanner Staging, 146 (40.3%) subjects who were not already at Tanner Stage 5 (adult sexual maturity) progress at least 1 stage from baseline as of the last assessment during the open-label treatment phase. A total of 132 de novo subjects (79 of 210 [37.6%] male subjects and 53 of 152 [34.9%] female subjects) were already at Tanner Stage 5 at baseline. Tanner Staging progression (i.e., 1 to 3 stages from baseline) was similar for male and female de novo subjects during aripiprazole treatment (87 of 210 [41.4%] male subjects and 59 of 152 [38.8%] female subjects).

Laboratory findings

No clinically meaningful changes from baseline were observed in serum chemistry, haematology, urine analysis and other laboratory test parameters in the open-label treatment phase of trial 31-09-266.

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). The prolactin baseline mean for the aripiprazole group was 4.26, and the last visit mean was 6.29. The prolactin baseline mean for the placebo group was 4.43, and the last visit mean was 9.79. 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 blood insulin in 2 (2.0%) subjects each. All other clinical laboratory test TEAEs were reported by 1 subject in either treatment group.

Safety related to drug-drug interactions and other interactions

385 of 510 (75.5%) subjects in the Open-label Treatment Phase Enrolled Sample used at least one concomitant medication prior to the start of the trial period, with incidences of use by de novo subjects and rollover subjects of 357 of 362 [98.6%] subjects and 28 of 148 [18.9%] subjects, respectively. The most frequently administered classes of medications prior to the start of the trial period for de novo subjects included psycholeptics (98.1%), anti-Parkinson drugs (19.1%), antiepileptics (16.3%), and psychoanaleptics (15.7%). The most frequently administered medications for de novo subjects prior to the start of the trial period were risperidone (40.3%) and aripiprazole (29.0%). 274 of 283 (96.8%) subjects in the Open-label Treatment Phase Enrolled Sample used at least one concomitant medication in the conversion phase, with incidences for de novo subjects and rollover subjects of 273 of 280 (97.5%) subjects and 1 of 3 (33.3%) subjects, respectively.. The most frequently administered classes of medications for de novo subjects during the conversion phase included psycholeptics (95.7%), anti-Parkinson drugs (22.9%), and antiepileptics (11.8%). The most frequently administered medications for de novo subjects during the conversion phase were risperidone (46.8%) and olanzapine (14.3%). 318 of 510 (62.4%) subjects in the Open-label Treatment Phase Enrolled Sample used at least one concomitant medication during the open-label treatment phase, with incidences of use by de novo subjects and rollover subjects of 255 of 362 (70.4%) subjects and 63 of 148 (42.6%) subjects, respectively. The most frequently administered classes of medications for de novo subjects during the open-label treatment phase included psycholeptics (33.1%), analgesics (21.0%), psychoanaleptics (17.7%), anti-Parkinson drugs (17.4%), antiepileptics (16.0%), and antibacterial for systemic use (12.2%). The most frequently administered medication for de novo subjects

during the open-label treatment phase was paracetamol (16.6%). 427 of 510 (83.7%) subjects in the Open-label Treatment Phase Enrolled Sample used at least one concomitant medication after the end of the trial period, with incidences of use by de novo subjects and rollover subjects of 316 of 362 (87.3%) subjects and 111 of 148 (75.0%) subjects, respectively.

Discontinuation due to adverse events

The main reason for discontinuation from the trial was the sponsor discontinuing the trial (180 subjects [89.6%] total), which occurred after the 37th event of exacerbation of psychotic symptoms/impending relapse occurred. There was no detailed information about discontinuation due to AEs in the information provided.

Study 31-09-267

Patient exposure

All subjects in trial 31-09-267 receiving at least 1 dose of IMP were included in the safety dataset. 510 subjects were exposed to at least 1 dose of aripiprazole in the open-label treatment phase at a mean (SD) daily dose of 18.1 (6.9) mg. The mean daily doses were the same for de novo and rollover subjects. A total of 273 of 362 (75.4%) de novo subjects received > 372 to 776 days of aripiprazole treatment in the open-label treatment phase. A total of 158 de novo subjects participated in the trial for more than 728 days: 127 subjects with schizophrenia and 31 subjects with bipolar disorder. De novo subjects were allowed 24 months of treatment in the open-label treatment phase while rollover subjects were only allowed a maximum of 12 months; thus, the mean (SD) aripiprazole treatment for de novo subjects was 547.9 (237.7) days. 70 of 362 de novo subjects ended treatment on a daily dose of 30 mg. The majority of subjects with bipolar disorder ended treatment in the open-label treatment phase on a dose of 10 to 20 mg, whereas subjects with schizophrenia were fairly evenly distributed between doses of 10 to 30 mg. In the conversion phase, 294 de novo subjects received a mean (SD) daily dose of 12.5 (3.2) mg aripiprazole. Subjects with schizophrenia and bipolar disorder received mean (SD) daily doses of 12.8 (3.1) mg and 10.7 (3.0) mg, respectively.

A total of 524 subjects entered this trial (297 subjects in the conversion phase and 510 subjects in the open-label treatment phase). Overall, in the open-label treatment phase, 362 subjects were de novo subjects (280 subjects entered into the conversion phase) and 148 subjects rolled over from Trial 31-09-266 (3 subjects enrolled in the conversion phase prior to entering the open-label treatment phase). The number of subjects with schizophrenia that entered this trial at any phase was 427 and the number of subjects with bipolar disorder that entered this trial at any phase was 97. All of the subjects were analysed for safety (524 subjects) and 507 of 510 (99.4%) subjects in the open-label treatment phase were analysed for efficacy. A total of 158 de novo subjects participated in the trial for more than 728 days: 127 with schizophrenia and 31 with bipolar disorder. The de novo subset of the subject population is the primary dataset for the PIP commitment. Only 198 of 524 (37.8%) subjects completed the trial; 14 of 297 (4.7%) subjects discontinued during the conversion phase and 312 of 510 (61.2%) subjects discontinued from the open-label treatment phase. De novo and rollover subjects discontinued from the open-label treatment phase at rates of 185 of 362 (51.1%) subjects and 127 of 148 [85.8%] subjects, respectively. Subjects with bipolar disorder and subjects with schizophrenia discontinued from the open-label treatment phase at similar rates (59 of 94 [62.8%] subjects and 253 of 416 [60.8%] subjects, respectively). The most frequent reasons for subject discontinuation during any phase were sponsor discontinued trial (31.5%), subject withdrew consent (13.7%), and AE (6.9%). Most of the premature study discontinuations were from the open-label treatment phase rather than from the conversion phase. Of the most frequent reasons for subject discontinuation, de novo subjects and rollover subjects discontinued from the open-label treatment phase because the sponsor discontinued trial (16.3% and 71.6%, respectively). De novo and rollover subjects discontinued from the open-label treatment phase due to subject withdrew consent at rates of 14.4% and 8.8%, respectively, and due to AEs at rates of 7.7% and 3.4%, respectively. Of the most frequent reasons for subject discontinuation, schizophrenia subjects and bipolar subjects discontinued from the open-label treatment phase because sponsor discontinued trial at rates of 38.2% and 6.4%, respectively, and subjects with schizophrenia or bipolar disorder discontinued from the open-label treatment phase due to subject withdrew consent at rates of 11.8% and 17.0%, respectively). For all subjects, the most frequent reason for withdrawal of consent was the refusal of subjects who had just turned 18 years of age to sign the ICF.
Only de novo subjects had up to 2 years of exposure, rollover subjects had up to 1 year of exposure. The de novo portion of the dataset is intended to address the PIP commitment, as described above; rollover subjects received open-label treatment after the participation of the placebo-controlled study in a compassionate use basis. The length of exposure is different between the de novo and rollover cohorts;

therefore, the emphasis in this report is on the de novo subject data.

Table: subject disposition 31-09-267

Subjects	Conversion Phase N=297 N (%)	Open-label Treatment Phase N=510 N (%)	Total N=524 N (%)
Screened	-	-	619
Screen failure	-	-	95
Entered	297 (100.0)	510 (100.0)	524 (100.0)
Discontinued	14 (4.7)	312 (61.2)	326 (62.2)
Lost to follow up	0 (0.0)	21 (4.1)	21 (4.0)
Adverse event	3 (1.0)	33 (6.5)	36 (6.9)
Sponsor discontinued trial	0 (0.0)	165 (32.4)	165 (31.5)
Subject met withdrawal criteria	1 (0.3)	9 (1.8)	10 (1.9)
Subject was withdrawn by investigator	2 (0.7)	12 (2.4)	14 (2.7)
Subject withdrew consent	7 (2.4)	65 (12.7)	72 (13.7)
Protocol deviation	1 (0.3)	0 (0.0)	1 (0.2)
Lack of efficacy as determined by the investigator	0 (0.0)	7 (1.4)	7 (1.3)
Completed[a]	-	198 (38.8)	198 (37.8)
Entered next phase	283 (95.3)	-	-
Analyzed for safety[b]	297 (100.0)	510 (100.0)	-
Analyzed for efficacy[c]	-	507 (99.4)	-

Note: Percentages are based on the number of subjects in the safety sample of the corresponding phase. For the total group, percentages are based on number of subjects in the enrolled sample.

[a]De novo subjects who completed the open-label treatment phase Month 24 visit or rollover subjects from Trial 31-09-266 who completed open-label treatment phase Month 12 visit.

[b]Subjects who received at least one dose of trial medication in the corresponding phase were included in the safety analysis.

[c]Subjects who received at least one dose of trial medication and were evaluated for at least one efficacy endpoint in the corresponding phase were included in the efficacy analysis.

Table: Subject disposition in open label phase

Subjects	Enrolment Source		Target Disease		Total
	De Novo N=362 N (%)	Trial 31-09-266 Rollover N=148 N (%)	Bipolar Disorder N=94 N (%)	Schizophrenia N=416 N (%)	N=510 N (%)
Entered	362 (100.0)	148 (100.0)	94 (100.0)	416 (100.0)	510 (100.0)
Discontinued	185 (51.1)	127 (85.8)	59 (62.8)	253 (60.8)	312 (61.2)
Lost to follow up	21 (5.8)	0 (0.)	16 (17.0)	5 (1.2)	21 (4.1)
Adverse event	28 (7.7)	5 (3.4)	7 (7.4)	26 (6.3)	33 (6.5)
Sponsor discontinued trial	59 (16.3)	106 (71.6)	6 (6.4)	159 (38.2)	165 (32.4)
Subject met withdrawal criteria	9 (2.5)	0 (0.0)	7 (7.4)	2 (0.5)	9 (1.8)
Subject was withdrawn by investigator	12 (3.3)	0 (0.0)	5 (5.3)	7 (1.7)	12 (2.4)
Subject withdrew consent	52 (14.4)	13 (8.8)	16 (17.0)	49 (11.8)	65 (12.7)
Lack of efficacy as determined by the investigator	4 (1.1)	3 (2.0)	2 (2.1)	5 (1.2)	7 (1.4)
Completed[a]	177 (48.9)	21 (14.2)	35 (37.2)	163 (39.2)	198 (38.8)
Analysed for safety[b]	362 (100.0)	148 (100.0)	94 (100.0)	416 (100.0)	510 (100.0)
Analysed for efficacy[c]	360 (99.4)	147 (99.3)	93 (98.9)	414 (99.5)	507 (99.4)

Note: Percentages are based on the number of subjects in the safety sample of the open-label treatment phase. For the total group, percentages are based on number of subjects in the open-label treatment phase.

[a]De novo subjects who completed the open-label treatment phase Month 24 visit or rollover subjects from Trial 31-09-266 who completed open-label treatment phase Month 12 visit.

[b]Subjects who received at least one dose of trial medication in the corresponding phase were included in the safety analysis.

[c]Subjects who received at least one dose of trial medication and were evaluated for at least one efficacy endpoint in the corresponding phase were included in the efficacy analysis.

A total of 409 of 510 subjects who entered the open-label treatment phase were from non-US sites. Of these, the countries from which the most subjects entered the open-label treatment phase included Ukraine

(94 subjects), India (90 subjects), the Russian Federation (73 subjects), and Bulgaria (69 subjects).

Table: subject enrolment per country

Country	Screened N	Conversion Phase N	Open-label Treatment Phase N
Bulgaria	76	60	69
Croatia	9	7	6
Hungary	12	10	11
India	111	56	90
Philippines	12	1	12
Poland	29	15	24
Romania	17	0	17
Russian Federation	73	0	73
Serbia	16	12	12
Taiwan, Province of China	1	0	1
Ukraine	106	98	94
United States	157	38	101
Total	619	297	510

Overall, 172 of 297 (57.9%) subjects were enrolled in the conversion phase for 43 to 50 days (all 172 subjects were de novo subjects). The incidence of bipolar and schizophrenic subjects who enrolled in the conversion phase for 43 to 50 days was 23 of 43 (53.5%) and 149 of 254 (58.7%), respectively. A total of 298 of 510 (58.4%) subjects were enrolled in the open-label treatment phase for at least 12 months (365 to 378 days), including 18 of 148 (12.2%) rollover subjects and 280 of 362 (77.3%) de novo subjects. Of these 298 subjects, 58 of 94 (61.7%) subjects had bipolar disorder and 240 of 416 (57.7%) subjects had a diagnosis of schizophrenia. One hundred fifty-eight of 362 (43.6%) de novo subjects were enrolled in the open-label treatment phase for the maximum time allowed (> 728 to 777 days); rollover subjects were only permitted a maximum of 12 months of treatment in the open-label treatment phase. Of these 158 subjects, 31 of 94 (33.0%) subjects with bipolar disorder and 127 of 416 (30.5%) subjects with schizophrenia remained in the trial for the 2-year interval.

Adverse events

In trial 31-09-267, 349 of 510 (68.4%) subjects experienced a total of 1156 TEAEs. The incidence of TEAEs among de novo subjects was 278 of 362 (76.8%) subjects and the incidence of TEAEs among rollover subjects was 71 of 148 (48.0%) subjects. A total of 49 of 510 (9.6%) subjects experienced at least 1 serious TEAE. The rates of serious and severe TEAEs among de novo subjects were 42 of 362 (11.6%) subjects and 30 of 362 (8.3%) subjects, respectively, and for rollover subjects were 7 of 148 (4.7%) subjects and 3 of 148 (2.0%) subjects, respectively. A total of 32 of 510 (6.3%) subjects discontinued the trial medication due to an AE. The incidence of de novo and rollover subjects who discontinued trial medication due to AEs was 27 of 362 (7.5%) subjects and 5 of 148 (3.4%) subjects, respectively. In the conversion phase, 122 of 294 (41.5%) de novo subjects reported a TEAE. Two of 294 (0.7%) de novo subjects reported a serious TEAE and 3 of 294 (1.0%) de novo subjects discontinued the trial due to AEs.

Table: Summary of Adverse Events - (Open-label Treatment Phase Safety Sample)

Number of:	Enrolment Source		Total
	De Novo N=362 n (%)[a]	Trial 31-09-266 Rollover N=148 n (%)[a]	N=510 n (%)[a]
Subjects treated with aripiprazole oral tablets	362 (100.0)	148 (100.0)	510 (100.0)
Subject days of aripiprazole oral tablet exposure	197041	36298	233339
Subjects with AEs	278 (76.8)	71 (48.0)	349 (68.4)
Adverse events	1277	167	1444
Subjects with TEAEs	278 (76.8)	71 (48.0)	349 (68.4)
TEAEs[b]	1005	151	1156
Subjects with serious TEAEs	42 (11.6)	7 (4.7)	49 (9.6)
Subjects with severe TEAEs	30 (8.3)	3 (2.0)	33 (6.5)
Subjects discontinued trial medication due to AE	27 (7.5)	5 (3.4)	32 (6.3)

[a]Percentages are based on the number of subjects treated in the corresponding phase.
[b]A TEAE was defined as an AE that started after start of IMP treatment; or if the event was continuous from baseline and was serious, trial drug related, or resulted in death, discontinuation, interruption or reduction of IMP. Multiple occurrences of TEAEs were counted once, per specific MedDRA preferred term.

Common Adverse Events

In trial 31-09-267, 349 of 510 (68.4%) subjects experienced a total of 1156 TEAEs: 278 of 362 (76.8%) de novo subjects and 71 of 148 (48.0%) rollover subjects. A total of 49 of 510 (9.6%) subjects experienced at least 1 serious TEAE: 42 of 362 (11.6%) de novo subjects and 7 of 148 (4.7%) rollover subjects. A total of 203 of 510 (39.8%) subjects had at least 1 TEAE that was considered by the investigator to be potentially causally related to the IMP: 163 of 362 (45.0%) de novo subjects and 40 of 148 (27.0%) rollover subjects.

TEAEs

The most commonly reported TEAEs among de novo subjects were headache (61 of 362 [16.9%] subjects), schizophrenia (33 of 362 [9.1%] subjects), increased weight (32 of 362 [8.8%] subjects), anxiety (30 of 362 [8.3%] subjects), somnolence (30 of 362 [8.3%] subjects), and nasopharyngitis (29 of 362 [8.0%] subjects). In the conversion phase, the most commonly reported TEAEs in de novo subjects included headache (7.8%) and somnolence (6.8%).

Table: TEAE 31-09-267

MedDRA System Organ Class and Preferred Term	Enrolment Source		Total
	De Novo N=362 n (%)	Trial 31-09-266 Rollover N=148 n (%)	N=510 n (%)
Gastrointestinal Disorders			
Vomiting	28 (7.7)	2 (1.4)	30 (5.9)
General Disorders and Administration Site Conditions			
Irritability	21 (5.8)	0 (0.0)	21 (4.1)
Infections and Infestations			
Nasopharyngitis	29 (8.0)	5 (3.4)	34 (6.7)
Investigations			
Weight increased	32 (8.8)	6 (4.1)	38 (7.5)
Nervous System Disorders			
Headache	61 (16.9)	6 (4.1)	67 (13.1)
Somnolence	30 (8.3)	3 (2.0)	33 (6.5)
Tremor	20 (5.5)	1 (0.7)	21 (4.1)
Psychiatric Disorders			
Schizophrenia	33 (9.1)	9 (6.1)	42 (8.2)
Anxiety	30 (8.3)	2 (1.4)	32 (6.3)

Note: A TEAE was defined as an AE that started after start of IMP treatment; or if the event was continuous from baseline and was serious, IMP related, or resulted in death, discontinuation, interruption or reduction of IMP. Subjects were counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

Table: Incidence of TEAEs Considered by the Investigator as Potentially Causally Related to the IMP and Occurring in Greater Than or Equal to 5% of Subjects (Open-label Treatment Phase Safety Sample)

MedDRA System Organ Class and Preferred Term	Enrolment Source		Total
	De Novo N=362 n (%)	Trial 31-09-266 Rollover N=148 n (%)	N=510 n (%)
Investigations			
Weight increased	25 (6.9%)	5 (3.4%)	30 (5.9%)
Nervous System Disorders			
Headache	27 (7.5%)	2 (1.4%)	29 (5.7%)
Somnolence	26 (7.2%)	3 (2.0%)	29 (5.7%)
Tremor	18 (5.0%)	1 (0.7%)	19 (3.7%)

Note: A TEAE was defined as an AE that started after start of IMP treatment; or if the event was continuous from baseline and was serious, IMP related, or resulted in death, discontinuation, interruption or reduction of IMP. Subjects were counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

Serious adverse event / deaths / other significant events

Deaths

The 1 death (accidental acute heroin toxicity in a de novo subject) that occurred during trial 31-09-267 was not suicide-related and unrelated to trial drug. On Day 572 of the open-label treatment phase, the subject died of accidental acute heroin toxicity (MedDRA preferred term: toxicity to various agents). The s-ubject, a 17-year-old white male, was a de novo subject with a diagnosis of bipolar disorder. The subject had a negative drug screen at screening and baseline, but tested positive for cocaine/metabol and tetrahydrocannabinol at Month 3. A retest was negative as well as the Month 6 drug screen. The subject then tested positive for tetrahydrocannabinol at Month 9, 12, and 15. Morphine was also detected at Month 12. After the third consecutive positive tetrahydrocannabinoil result, the clinical team held a case conference

and detailed the clinical picture and management plan in a note to file. The subject was not deemed to have met substance dependence criteria. Cannabis use was reported as sporadic and due to contextual factors. The subject had insomnia, was working unsociable hours, and sharing a flat with friends who smoked cannabis. The subject had recently moved back home. At the last visit, prior to the subject's death (10 days before), drug screen was negative for tetrahydrocannabinol. The PI did not believe that the subject met withdrawal criteria based on his illicit drug use. The subject was counselled on the use of these drugs while participating in the trial. On Day 572, the subject had been found nonresponsive in his bed; emergency services were called and the subject was taken to the hospital. The subject was reportedly alive during transport and died at the hospital. He had been healthy and did not report any suicidal thoughts. Ongoing concomitant medication included trazodone hydrochloride and lisdexamfetamine mesylate. An autopsy provided the following pathological diagnoses: acute and chronic prescription drug and illicit drug abuse with acute heroin toxicity; haemorrhages and puncture marks in the right antecubital fossa; history of alprazolam abuse; pulmonary oedema; hypertensive cardiovascular disease with cardiac hypertrophy (450 g). Femoral blood specimen noted 6-monoacetylmorphine < 0.01 mg/L, codeine 0.01 mg/L, marijuana metabolite was presumptive positive, and morphine 0.12 mg/L. Stomach contents specimen revealed 6-monoacetylmorphine < 0.25 mg/L, codeine 0.43 mg/L, and morphine 2.5 mg/L. Urine specimen showed 6-monoacetylmorphine 1.5 mg/L, codeine 0.17 mg/L, and morphine > 2.0 mg/L. The fatal TEAE was considered severe and unrelated to trial medication.

Other SAEs

Serious TEAEs were reported for a total of 49 of 510 (9.6%) subjects. The incidence of serious TEAEs for de novo subjects and rollover subjects were 42 of 362 (11.6%) subjects and 7 of 148 (4.7%) subjects, respectively. The most frequently reported serious TEAEs in de novo subjects were schizophrenia (14 of 362 [3.9%] subjects), suicidal ideation (8 of 362 [2.2%] in subjects), bipolar disorder (7 of 362 [1.9%] subjects), aggression (3 of 362 [0.8%] subjects), agitation (2 of 362 [0.6%] subjects), and auditory hallucination (2 of 362 [0.6%] subjects). All serious TEAEs of suicidal ideation were reported for de novo subjects. In the conversion phase, serious TEAEs were reported for 2 de novo subjects: tooth disorder was reported for a subject with schizophrenia and bipolar I disorder for a subjects with bipolar disorder.

Table: Incidence of Serious Treatment-emergent Adverse Events - (Open-label Treatment Phase Safety Sample)

MedDRA System Organ Class and Preferred Term	Enrolment Source		Total
	De Novo N=362 N (%)	Trial 31-09-266 Rollover N=148 N (%)	N=510 N (%)
Total[a]	42 (11.6)	7 (4.7)	49 (9.6)
Congenital, Familial and Genetic Disorders			
Gilbert's syndrome	1 (0.3)	0 (0.0)	1 (0.2)
Gastrointestinal Disorders			
Gastritis	0 (0.0)	1 (0.7)	1 (0.2)
General Disorders and Administration Site Conditions			
Irritability	1 (0.3)	0 (0.0)	1 (0.2)
Infections and Infestations			
Laryngitis	1 (0.3)	0 (0.0)	1 (0.2)
Tuberculosis	1 (0.3)	0 (0.0)	1 (0.2)
Injury, Poisoning and Procedural Complications			
Intentional overdose	1 (0.3)	0 (0.0)	1 (0.2)
Toxicity to various agents	1 (0.3)	0 (0.0)	1 (0.2)
Investigations			
Blood creatine phosphokinase increased	1 (0.3)	0 (0.0)	1 (0.2)

Metabolism and Nutrition Disorders			
Decreased appetite	1 (0.3)	0 (0.0)	1 (0.2)
Psychiatric Disorders			
Schizophrenia	14 (3.9)	4 (2.7)	18 (3.5)
Suicidal ideation	8 (2.2)	0 (0.0)	8 (1.6)
Bipolar disorder	7 (1.9)	0 (0.0)	7 (1.4)
Aggression	3 (0.8)	0 (0.0)	3 (0.6)
Agitation	2 (0.6)	1 (0.7)	3 (0.6)
Hallucination, auditory	2 (0.6)	0 (0.0)	2 (0.4)
Suicide attempt	1 (0.3)	1 (0.7)	2 (0.4)
Bipolar I disorder	1 (0.3)	0 (0.0)	1 (0.2)
Depression	1 (0.3)	0 (0.0)	1 (0.2)
Mania	1 (0.3)	0 (0.0)	1 (0.2)
Mental status changes	0 (0.0)	1 (0.7)	1 (0.2)
Mood swings	1 (0.3)	0 (0.0)	1 (0.2)
Psychotic disorder	0 (0.0)	1 (0.7)	1 (0.2)
Self injurious behaviour	1 (0.3)	0 (0.0)	1 (0.2)
Reproductive System and Breast Disorders			
Metrorrhagia	1 (0.3)	0 (0.0)	1 (0.2)

Note: A TEAE was defined as an AE that started after start of IMP treatment; or if the event was continuous from baseline and was serious, IMP related, or resulted in death, discontinuation, interruption or reduction of IMP. Subjects were counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.
[a]Subjects with AEs in multiple system organ classes were counted only once towards the total.

Other significant AEs

Adverse events of special interest for trial 31-09-267 are described in detail below.

Extrapyramidal Symptoms

Overall, in the open-label treatment phase, EPS-related TEAEs were reported for 58 of 510 (11.4%) subjects: 48 of 362 (13.3%) de novo subjects and 10 of 148 (6.8%) rollover subjects. The most frequently reported EPS-related TEAEs for de novo subjects were akathisia (17 of 362 [4.7%] subjects) and extrapyramidal disorder (15 of 362 [4.1%] subjects). No EPS-related TEAEs were serious or led to the discontinuation of trial medication.

Orthostasis

A total of 5 of 510 (1.0%) subjects experienced orthostasis-related TEAEs in the open-label treatment phase (5 of 362 [1.4%] de novo subjects). The TEAEs included syncope (3 of 362 [0.8%] de novo subjects) and orthostatic hypotension (2 of 263 [0.6%] de novo subjects). The events were not serious and did not result in the discontinuation of trial medication.

Suicide

A total of 17 of 510 (3.3%) subjects experienced suicide-related TEAEs in the open-label treatment phase: 14 of 362 (3.9%) de novo subjects and 3 of 148 (2.0%) rollover subjects.

The most frequently reported suicide-related TEAE for de novo subjects was suicidal ideation, which was reported for 9 of 362 (2.5%) subjects. Serious TEAEs that were reported for de novo subjects included suicide attempt (1 of 362 [0.3%] subjects), suicidal ideation (8 of 362 [2.2%] subjects with 1 of these TEAEs considered to be potentially causally related to IMP), and intentional overdose. Three of these serious TEAEs led to the discontinuation of trial medication (suicidal ideation for 2 of 362 [0.6%] subjects and intentional overdose for 1 of 362 [0.3%] subjects. Of note, the death that occurred in this trial was not suicide related.

Sedation and Somnolence

A total of 37 of 510 (7.3%) subjects experienced a sedation- or somnolence-related TEAE during the open-label treatment phase: 34 of 362 (9.4%) de novo subjects and 3 of 148 (2.0%) rollover subjects. Somnolence was more prevalent than sedation (30 of 362 [8.3%] de novo subjects and 4 of 362 [1.1%] de novo subjects, respectively). No sedation or somnolence-related TEAEs were serious or resulted in the discontinuation of IMP.

Glucose

In the open-label treatment phase, glucose-related TEAEs were reported for only 2 of 510 (0.4%) subjects. Both events were reported in de novo subjects. These TEAEs were increased blood glucose and metabolic syndrome. None of the TEAEs related to glucose levels were serious or resulted in the discontinuation of trial medication. All glucose-related TEAEs considered to be potentially causally related to IMP.

Lipid Parameters

In the open-label treatment phase, lipid parameter-related TEAEs were reported for 2 of 510 (0.4%) subjects. Both events were reported in de novo subjects. The lipid parameter-related TEAEs included increased high-density lipoprotein and hypercholesterolemia. None of the TEAEs related to lipid parameters were serious or resulted in the discontinuation of trial medication. All lipids parameter-related TEAEs were considered to be potentially causally related to IMP.

Weight Gain

A total of 52 of 510 (10.2%) subjects experienced a weight gain-related TEAE in the open-label treatment phase: 43 of 362 (11.9%) de novo subjects and 9 of 148 (6.1%) rollover subjects. The most frequently reported weight-gain TEAE for de novo subjects was increased weight (32 of 362 [8.8%] subjects). None of the TEAEs related to weight gain in de novo subjects were serious; however, one TEAE of increased weight resulted in the discontinuation of trial medication.

Prolactin

In the open-label treatment phase, prolactin-related TEAEs were reported for 3 of 510 (0.6%) subjects: 1 of 362 (0.3%) de novo subjects and 2 of 148 (1.4%) rollover subjects. The prolactin-related TEAE of increased blood prolactin was reported for 1 of 362 (0.3%) de novo subjects with schizophrenia (female). This event was not serious and did not result in discontinuation of trial medication.

Hepatic

Hepatic-related TEAEs were reported for 4 of 510 (0.8%) subjects in the open-label treatment phase: 3 of 362 (0.8%) de novo subjects and 1 of 148 (0.7%) rollover subjects. The hepatic-related TEAEs reported by de novo subjects included increased ALT (1 of 362 [0.3%] subjects) and increased blood bilirubin (2 of 362 [0.6%] subjects). These events did not result in discontinuation of trial medication.

New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment

In the double-blind maintenance, similar frequencies of signs and symptoms of cognitive side effects were seen for the aripiprazole-treated subjects and placebo-treated subjects. The sign/symptom with the largest difference between treatment groups was for adverse effects on reasoning and problem solving (61 [62.2%] subjects in the aripiprazole group and 34 [70.8%] subjects in the placebo group). No notable changes from baseline by week were seen for the NY-AACENT total score of drug-related, mild, function impaired signs or symptoms in the OC dataset. No notable changes from baseline by week were seen for the NY-AACENT total score of drug-related, moderate, function impaired signs or symptoms in the OC dataset. In general, the NY-AACENT scale could not distinguish between cognitive side effects due to schizophrenia or due to the use of neuroleptics. There was no apparent drug-relationship for cognitive side effects.

Columbia-Suicide Severity Rating Scale

There were no completed suicides in trial 31-09-266. During the open-label treatment phase, suicidality was reported on the C-SSRS by 30 of 360 (8.3%) de novo subjects and suicidal ideation was reported by 29 of 360 (8.1%) de novo subjects. Worsening and emergence of suicidal ideation was reported by 25 of 360 (6.9%) de novo subjects and 18 of 360 (5.0%) de novo subjects, respectively. For the open-label treatment phase, based on the C-SSRS, actual suicide attempts were reported for 2 of 360 (0.6%) de novo subjects, interrupted attempts were reported for 1 of 360 (0.3%) de novo subjects, and preparatory acts or behaviour was reported for 1 of 360 (0.3%) de novo subjects. Suicidal ideation for de novo subjects during the open-label treatment period included wish to be dead (24 of 360 [6.7%] subjects), nonspecific active suicidal thoughts (18 of 360 [5.0%] subjects), active suicidal ideation without intent to act (11 of 360 [3.1%] subjects), active suicidal ideation with some intent to act but without a specific plan (7 of 360 [1.9%] subjects), and active suicidal ideation with a specific plan and intent (1 of 360 [0.3%] subjects). During the conversion and open-label treatment phases, the mean C-SSRS Suicidal Ideation Intensity Total Score decreased from baseline to approximately 0 at Week 1 and generally remained steady throughout the phase overall and for most groups. The mean change from baseline in suicidal ideation intensity total score was = 0.0 at all visits for both treatment groups in trial 31-09-267.

Tanner Staging

Of 98 aripiprazole-treated subjects with baseline and follow-up Tanner staging, 26 (26.5%) progressed 1 or 2 stages from baseline as of the last assessment. Of 48 placebo-treated subjects with baseline and follow-up Tanner staging, 8 (16.7%) progressed 1 or 2 stages as of the last assessment.

Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire

In the double-blind maintenance phase of trial 31-09-267, there was no statistical difference between treatment groups in the mean change from baseline in P-QLES-Q total score by week for the LOCF and OC datasets. Similar results were seen in the adjusted mean change from baseline in P-QLES-Q total score by week for the LOCF and OC datasets. 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 findings

No clinically meaningful changes from baseline were observed in serum chemistry, haematology, urine analysis and other laboratory test parameters in the double-blind maintenance phase of trial 31-09-267.

The most frequently reported incidences of potentially clinically relevant chemistry values for de novo subjects were chloride (133 of 358 [37.2%] subjects, inorganic phosphorus (106 of 359 [29.5%] subjects), and fasting HDL cholesterol (94 of 348 [27.0%] subjects). No abnormal haematology results of potential clinical relevance were reported for more than 5% of subjects overall. The most frequently reported potentially clinically relevant urinalysis parameters for de novo subjects were urine protein (259 of 351 [73.8%] subjects) and specific gravity (139 of 360 [38.6%] subjects). The most frequently reported potentially clinically relevant other laboratory assessment for de novo subjects was prolactin (236 of 360 [65.6%] subjects. Prolactin levels > 2 × ULN at any post-baseline visit were reported for 13 of 360 (3.6%) de novo subjects (9 female and 4 male subjects); all subjects had a diagnosis of schizophrenia. Prolactin levels > 3 × ULN at any post-baseline visit were reported for 6 of 360 (1.7%) de novo subjects (all female subjects); all subjects had schizophrenia. The most frequently reported clinical laboratory-related TEAEs for de novo subjects were increased blood CPK (7 of 362 [1.9%] subjects) and proteinuria (4 of 362 [1.1%] subjects). One potential Hy's law case was reported during this trial. On Day 48 of the open-label treatment phase, Subject 139-0074, a 16-year-old male with schizophrenia, who had previously received aripiprazole for 4 months in Trial 31-09-266, had potentially clinically relevant elevations in ALT (483 U/L; ULN: 43 U/L), AST (253 U/L; ULN: 40 U/L), and total bilirubin (5.3 mg/dL; ULN: 1.2 mg/dL). On Day 46, a TEAE of hepatitis A was reported for this subject. The TEAE was mild in severity, was not considered by the investigator to be causally related to IMP, and resulted in the discontinuation of trial medication.

Vital Signs, Physical Findings, and Other Observations Related to Safety

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. This was not unexpected, as weight gain is a known side effect of aripiprazole. Of the subjects who gained ⩾ 7 % during the double-blind maintenance phase, 16 aripiprazole subjects and 4 placebo subjects had low BMI (< 23 kg/m2) at baseline, 2 aripiprazole subjects and 0 placebo subjects had average BMI (⩾ 23 - ⩽ 27 kg/m2) at baseline and 2 aripiprazole subjects and 0 placebo subjects had higher than average BMI (> 27 kg/m2) at baseline. Thus, the majority of the subjects who gained more than 7% weight from baseline to last visit had low BMI. This finding is similar to the analysis of weight increase in other paediatric programs. A total of 15 (10.3%) subjects reported a potentially clinically relevant increase ⩾ 15 mmHg in standing diastolic blood pressure: 11 (11.2%) subjects in the aripiprazole group and 4 (8.3%) subjects in the placebo group. All other incidences of vital signs of potential clinical relevance were reported by fewer than 8% of subjects in either treatment group. Potentially clinically relevant vital signs were comparable for the aripiprazole and placebo groups.

The most frequently reported TEAE related to vital signs was weight increased reported by 8 (8.2%) subjects in the aripiprazole group and 5 (10.4%) subjects in the placebo group. All other TEAEs related to vital signs were reported by 2 or fewer subjects in the aripiprazole group.

Incidence of weight gain (⩾ 7 % change from baseline) was 14.3% in the aripiprazole group compared to 8.3% in the placebo group at last visit. Weight loss (⩾ 7 % change from baseline) was comparable between the aripiprazole and placebo groups. Weight changes were in line with aripiprazole paediatric data for subjects aged 13 to 17 years.

Electrocardiogram

No clinically meaningful changes from baseline were observed in 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. Electrocardiogram-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 and 2 (2.0%) subjects in the aripiprazole group reported a TEAE of tachycardia. Two (2.0%) subjects in the aripiprazole group reported a TEAE of arrhythmia. All other ECG-related TEAEs were reported by 1 (1.0%) subject in the aripiprazole group.

Safety in special populations

Pregnancy

Two pregnancies were reported during the trial. Subject 619-5402, a de novo subject, became pregnant during the trial while taking oral contraceptives; the last dose of trial medication was taken on Day 174, after learning of the pregnancy. She delivered a healthy male infant by spontaneous vaginal delivery at gestational age of 40 weeks after an unremarkable pregnancy. The birth was uncomplicated; however, there was a period of physiological jaundice. At the infant's 4-month check-up, the child had reached all normal developmental milestones.

Subject 617-5069, a de novo subject, was sexually assaulted and became pregnant during the trial; the last dose of trial medication was taken on Day 260, after learning of the pregnancy. The subject gave birth to a female infant by spontaneous vacuum-assisted vaginal delivery at gestational age 38.4 weeks. The new-born had the umbilical cord wrapped 3 times around her leg, a caput succedaneum, a large middle digit on the right hand, bilateral wrist drop, upper extremity increased tone, and lower extremity decreased tone. There were no further updates to the condition of either mother or child.

Safety related to drug-drug interactions and other interactions

Concomitant Medications

A larger number and percentage of subjects in the aripiprazole group received concomitant medication during the double-blind maintenance than in the placebo group, 43 (43.9%) subjects compared to 17 (35.4%), respectively. The most frequently taken concomitant medications during the double-blind maintenance were trihexyphenidyl (6 [6.1%] subjects in the aripiprazole group and 5 [10.4%] subjects in the placebo group), paracetamol (11 [11.2%] subjects in the aripiprazole group and 3 [6.3%] subjects in

the placebo group), and clonazepam (6 [6.1%] subjects in the aripiprazole group and 4 [8.3%] subjects in the placebo group). All other concomitant medications were taken by 12% or less of subjects. During the double-blind maintenance, the mean (SD) average daily dose of anticholinergic agents (as mg benztropine equivalents) was 1.38 (1.05) in the aripiprazole group and 0.83 (0.74) for the placebo group. The mean (SD) average daily dose of benzodiazepine derivatives during the double-blind maintenance (as mg lorazepam equivalents) was 1.59 (1.50) in the aripiprazole group and 0.70 (0.87) in the placebo group.

Overdose

In Trial 31-09-267, one death of accidental overdose (MedDRA preferred term: toxicity to various agents) was reported and was not suicide-related.

Drug Abuse

No clinical trials were conducted to evaluate aripiprazole potential for abuse, tolerance, or physical dependence

Withdrawal and Rebound

No trials were conducted to assess withdrawal and rebound. Adverse events were followed for 30 days after stopping IMP.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No trials were conducted to assess effects on ability to drive or operate machinery or impairment of mental ability.

Discontinuation due to adverse events

The incidence of TEAEs resulting in discontinuation of the IMP was lower in the younger versus the older subgroup (4.5% vs 8.8%, respectively). The TEAEs resulting in discontinuation of the IMP for more than one subject overall included schizophrenia, which was more frequent among the older paediatric subjects, and suicidal ideation, which occurred for one subject in both age subgroups.

Table Trial 31-09-267: Incidence of TEAEs Resulting in Discontinuation of IMP (OL Treatment Phase Safety Sample, De Novo Subjects)

MedDRA Preferred Term	10 to 14 years (N=112)	15 to 17 years (N=250)	Total (N=362)
	n (%)		
Subjects Who Discontinued IMP Due to Any TEAE	**5 (4.5)**	**22 (8.8)**	**27 (7.5)**
Schizophrenia	2 (1.8)	16 (6.4)	18 (5.0)
Suicidal ideation	1 (0.9)	1 (0.4)	2 (0.6)
Aggression	1 (0.9)	0 (0.0)	1 (0.3)
Irritability	1 (0.9)	0 (0.0)	1 (0.3)
Mood swings	1 (0.9)	0 (0.0)	1 (0.3)
Blood creatine phosphokinase increased	0 (0.0)	1 (0.4)	1 (0.3)
Intentional overdose	0 (0.0)	1 (0.4)	1 (0.3)
Psychotic disorder	0 (0.0)	1 (0.4)	1 (0.3)
Self injurious behaviour	0 (0.0)	1 (0.4)	1 (0.3)
Weight decreased	0 (0.0)	1 (0.4)	1 (0.3)
Weight increased	0 (0.0)	1 (0.4)	1 (0.3)

Note: Results are sorted in descending order, by percentage in the total group. A TEAE was defined as an AE that started after start of IMP treatment; or if the AE was continuous from baseline and was serious, IMP related, or resulted in death, discontinuation, interruption or reduction of IMP.

3.2.1. Discussion on clinical safety

In Trial 31-09-267, safety was evaluated over 2 years in subjects with either bipolar disorder or schizophrenia.

Safety seemed generally comparable between the age subgroups (OL treatment phase, de novo subjects), and for the specific safety topics noted in the PIP:

- The overall incidence of TEAEs, as well as the incidence of those TEAEs considered serious or severe, was comparable across pediatric age subgroups. The incidence of AEs resulting in discontinuation of the IMP occurred less frequently for subjects in the younger subgroup (4.5%) versus the older subgroup (8.8%).
- Of TEAEs occurring in ≥ 5% of subjects in any age group, the younger subgroup had a higher (by at least 2-fold) incidence of oropharyngeal pain and aggression and a lower (by at least 2-fold) incidence of tremor, akathisia, and extrapyramidal disorder compared with the older pediatric subgroup.
- For serious TEAEs that occurred for > 2 subjects overall, the younger subgroup had a higher incidence (by at least 2-fold) of serious suicidal ideation and aggression and a lower incidence (by at least 2-fold) of serious schizophrenia compared with the older pediatric subgroup.
- Of the TEAEs of special interest:
    - Sedation/somnolence-related TEAEs occurred for 6.3% and 10.8% of subjects in the younger and older pediatric groups, respectively; most were events of somnolence.
    - Glucose-related TEAEs occurred infrequently in both age subgroups (1 subject per group). Of subjects with normal fasting insulin levels at baseline, levels were high at the last visit for 19/98 (19.4%) subjects in the younger group and 33/231 (14.3%) subjects in the older pediatric group.
    - Weight gain-related TEAEs occurred for 13.4% and 11.2% of subjects in the younger and older pediatric groups, respectively. No clinically meaningful changes from baseline were observed for weight or BMI as determined by an assessment of z-scores.
    - One subject in the older pediatric subgroup had a prolactin-related TEAE (blood prolactin increased).
    - Using the NY-AACENT, the incidence of adverse cognitive effects was comparable across age subgroups, with those effects relating to reasoning and problem solving being the most frequent (overall and in both the younger [71.4%] and older [60.0%] pediatric subgroups).
    - Of the 362 de novo subjects, 132 entered the trial at Tanner Stage 5. Of the remaining subjects, Tanner Stage progression was observed for: 5/5 (100%) subjects with Tanner 1 at baseline; 19/23 (82.6%) subjects with Tanner 2 at baseline; 44/62 (71.0%) subjects with Tanner 3 at baseline; and 78/140 (55.7%) subjects with Tanner 4 at baseline.

3.2.2. Conclusions on clinical safety

Study 31-09-266

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 presented 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 drug-induced liver events were reported. Weight and BMI changes were not presented on a case by case to assess clinical significance. Also, the global results between aripiprazole and placebo treatment in NY-AACENT scales are presented, but the entire results are not. Given the observed differences in study 31-09-267, the results from 266 study are expected to be relevant. There seems to be no delay in sexual maturation associated with aripiprazole treatment based on Tanner staging, but the number of young patients was low.

Due to the small study duration for most enrolled patients, long-term safety was not thoroughly assessed, particularly in the younger group, where a small number of patients was studied.

Study 31-09-267

Data on aripiprazole in adolescent patients with schizophrenia was provided. Safety was evaluated over 2 years in subjects with bipolar disorder and schizophrenia without any apparent loss of efficacy.

The most frequently reported AEs of special interest (7% to 12%) were EPS, weight gain, and sedation/somnolence-related TEAEs with suicide and orthostasis related TEAEs reported less frequently (1% to 4%). No NMS- or seizure related TEAEs were reported.

Weight and BMI data was presented on a patient basis, in order to admit them non clinically relevant, upon RfSI. Although there were no striking differences for most patients in the z-score of BMI / weight gain, the fact was that most patients were followed for a limited period of time – usually less than one year – and patients were not given enough time to increase weight / BMI.

Potentially clinically relevant findings for any type of ECG abnormality occurred in < 4% of subjects.

Overall, 42% of males and 37% of females entered the trial at Tanner Stage 5 (adult sexual maturity); 34% of males and 37% of females progress at least 1 stage as of the last assessment.

Study 31-09-267 does not allow a reliable safety assessment as selection occurs i.e. only patients who benefit and have no safety problems continue. The duration of the trial was very short to allow firm conclusions on discontinuation rates over time and reasons for discontinuation.

Children in the 10-14 age range are less prone to complain and report adverse events than adolescents 15-17. Even in the older age group, a significant number of patients refused to continue in the trial the moment they turned 18 years old and did not revalidate informed consent. During the procedure, the MAH discussed the rate of adverse events leading to discontinuation, the UKU scale and NY-AACENT scale in both 13-14 and 15-17 age groups, and found no relevant difference among groups in their response to aripiprazole vs placebo. The CHMP concluded that the behaviour was apparently similar in the magnitude of events, and that the explanation could be considered adequate.

3.2.3. PSUR cycle

The annex II related to the PSUR refers to the EURD list which remains unchanged.

3.3. Update of the Product information

As a consequence of this new indication, sections 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly.

4. Benefit-Risk Balance

Benefits

Beneficial effects

The design of the Study 31-09-266 allows for a comparison of Relapse rates as the main measure of beneficial effect. The point estimate for this endpoint favours Aripiprazole over Placebo both for the whole population studies (0.461) and for the patients aged 13 and 14 (0.495).

Uncertainty in the knowledge about the beneficial effects

Due to the low number or subjects (n = 41) and events (n = 11), the estimation of the HR in the subjects aged 13 and 14 years is extremely imprecise, with a 95% CI ranging from 0.151 to 1.628, not allowing for any firm conclusion on the existence (and on the direction) of a difference. This is confirmed by the log-rank test that fails, for this population, to reject the null hypothesis of absence of treatment effect (p = 0.2378).

Risks

Unfavourable effects and Uncertainty in the knowledge about the unfavourable effects

Adverse events cumulative over time such as weight gain independent of height growth are forcefully unidentified in a shorter than one year follow up duration. Moreover, considering that in bipolar disorder the PASS study showed that the lower age range had the higher risk for weight gain, the available evidence does not allow us to believe that younger schizophrenia paediatric patients would behave differently. However, the applicant has demonstrated that objective measures such as Z-scores showed limited changes.

In general, the short follow-up time and the small size limit the interpretability of the safety findings from study 31-09-266. The interpretability of the additional information in Study 31-09-267, additionally, could also be affected by the fact that part of the population on this study (30%) is somehow a selected subset of the population in the previous study (i.e. that only patients who benefit and have no safety problems continue in this study).

Effects Table

Table 3. Effects Table for Abilify in 13 and 14 years old subjects diagnosed with schizophrenia.

Effect	Short Description	Unit	Treatment	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Prevention of relapse	"Relapse" defined as exacerbation of symptoms or impending relapse	HR	0.495 (0.151 – 1.628)	1 (ref.)	Due to the low number or subjects (n = 41) and events (n = 11), the estimation of the HR is extremely imprecise. (p = 0.2378)	Study 31-09-266
Unfavourable Effects						
Weight gain		%	13.8	0	The small sample size and the short follow up do not allow to remove the uncertainties about safety.	Study 31-09-266

Discussion on the Benefit-Risk Balance

The CHMP acknowledged that schizophrenia is a rare condition in 13-14 years old of age, a population where there is an unmet need and where diagnosis can be difficult.

In study 266, the results differed between the 13-14 age range group and the 15-17 age range group. In particular, despite the point estimates of the hazard ratio of relapse were very similar (0.495 for 13 - 14 years old patients; 0.454, for 15 - 17 years old patients), the precision of these estimation – possibly also due to the small number (n= 41) of patients between 13 and 14 years - was different. While the 95% confidence interval for hazard ratio in older patients does not include the absence of treatment effect (0.242 to 0.879), it does not allow the same conclusion for the younger subgroup (0.151 1.628). This is consistent with the log-rank test that allows to refuse the hypothesis of absence of treatment effect for the older subgroup (p = 0.0161) but fails to do the same in the younger subgroup (p = 0.2378).

Concerns were also raised on the validity of the schizophrenia diagnosis in study 266 due to the very high remitter's rate in the short follow-up. This has been explained by the rate being actually a less-than-annual rate due to study discontinuation for sponsor's decision.

Moreover there were issues about external validity of the results as trials were carried out mostly outside EU, as in EU most IRB do not allow placebo trials in schizophrenia adolescents. Indeed 25% of patients in study 267 were from EU (all from Eastern Europe) and 12% in study 266 (albeit from a single country – Romania). A comparison between EU countries and the other world regions did not exhibit relevant differences. This comparison however was between Eastern Countries and the rest of the world, and not between EU non Eastern vs Eastern countries. So concern still remained on the generalizability of the results to the whole EU population

Moreover, the safety issues identified in children make the benefit-risk ratio even less positive in the younger age group. Data on safety was considered either too short or too directed towards ruling out adverse events. Patient number is both very short and shortly studied. At the best case scenario, in the medium term the most troublesome adverse events for children and adolescents seem to be less frequent in schizophrenia patients as compared to bipolar patients, but even this comparison must be considered with caution, as study duration and population refinement in the schizophrenia patients decrease the chance of TEAE as compared to the trial on bipolar patients.

Having reviewed the data provided by the company, and especially in view of the uncertainties, the CHMP considered that there was sufficient efficacy data to support the indication of 15 year old and above, but not in the 13-14 year old children.

However information of the withdrawal study (Trial 31-09-266) including specific information about the lower age ranges, might be important for physicians. Therefore, it was proposed to add the results of the randomised withdrawal study to section 5.1, to which the MAH agreed.

5. Recommendations

Outcome

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

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

Update of SmPC sections 4.8 and 5.1 to reflect clinical data generated in paediatric studies 31-09-266 and 31-09-267 submitted according to Article 46 of the paediatric regulation.

Paediatric data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMEA-000235-PIP02-10-M02 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC).