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EMA/CHMP/92268/2015
Committee for Medicinal Products for Human Use (CHMP)

Abilify

(Aripiprazole)

Procedure no.: EMEA/H/C/000471/P46 074

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

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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Administrative information

Invented name of the medicinal product:	Abilify
INN (or common name) of the active substance(s):	Aripiprazole
MAH:	Otsuka Pharmaceutical Europe Ltd.
Currently approved Indication(s):	Treatment of schizophrenia in adults and in adolescents aged 15 years and older. Treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment. Treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.
Pharmaco-therapeutic group (ATC Code):	N05AX12
Pharmaceutical form(s) and strength(s):	Tablets (5 mg, 10 mg, 15 mg, 30 mg) Orodispersible tablets (10 mg, 15 mg, 30 mg) Oral solution (1 mg/ml) Solution for injection (7.5 mg/ml)
Rapporteur:	Bruno Sepodes

1. Introduction

On 01-10-2014 the MAH submitted 3 completed paediatric study(ies) for aripiprazole, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study titles and numbers are stand alone studies.

2.2. Clinical aspects

2.2.1. Introduction

The clinical trials conducted to support this submission were performed in accordance with the principles of Good Clinical Practice, as defined by the International Conference on Harmonisation (ICH), and those carried out within the European Community met the ethical requirements of Directive 2001/20/EC.

Clinical trials carried out outside the European Union were conducted in accordance with the principles of Good Clinical Practice and the ethical requirements equivalent to the provisions of Directive 2001/20/EC.

The appended Table 1 shows all trials and third countries involved.

Table 1: Tabular Listing of Clinical Studies

Protocol No.	Title	Country	Report Location
31-10-272	A phase 3 multicentre, randomized, double-blind, placebo-controlled study enrolling subjects in Hungary, Canada, Taiwan, South Korea, Mexico, and the US to evaluate the safety and efficacy of flexible-dose QW oral aripiprazole in children and adolescents with TD	Hungary, Canada, Taiwan, South Korea, Mexico and the US	5.3.5.1
31-10-273	A phase 3 multicentre, randomized, double-blind, placebo-controlled study enrolling subjects in Bulgaria, Germany, Romania, Ukraine, and the US to evaluate the safety and efficacy of fixed-dose QW oral aripiprazole in Children and Adolescents with TD	Bulgaria, Germany, Romania, Ukraine and the US	5.3.5.1
31-10-274	A phase 3 open-label, multicentre study enrolling subjects in Bulgaria, Canada, Germany, Hungary, Mexico, Romania, South Korea, Taiwan, Ukraine, and the US to evaluate the long-term safety and tolerability of QW oral aripiprazole in children and adolescents with TD	Bulgaria, Canada, Germany, Hungary, Mexico, Romania, South Korea, Taiwan, Ukraine and the US	5.3.5.1

The MAH submitted final reports for:

- 31-10-272: A phase 3 multicentre, randomized, double-blind, placebo-controlled study, to evaluate the safety and efficacy of flexible-dose QW oral aripiprazole in children and adolescents with TD;
- 31-10-273: A phase 3 multicentre, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of fixed dose QW oral aripiprazole in Children and Adolescents with TD
- 31-10-274: A phase 3 open-label, multicentre study, to evaluate the long-term safety and tolerability of QW oral aripiprazole in children and adolescents with TD.

2.2.2. Clinical studies

Conduct of these trials is not a requirement of the Paediatric Investigation Plan for aripiprazole (EMEA-000235-PIP02-10-M02) and Otsuka Europe Development and Commercialisation Ltd. (OEDC) is not proposing a change to the aripiprazole Summary of Product Characteristics (SmPC) based upon these study results. Subsequently, the clinical development of the aripiprazole QW ECER formulation has been halted and there are no further development plans with this formulation.

31-10-272: A phase 3 multicentre, randomized, double-blind, placebo-controlled study, to evaluate the safety and efficacy of flexible-dose QW oral aripiprazole in children and adolescents with TD

Description

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of flexible-dose oral aripiprazole QW tablets in children and adolescents 7 to 17 years of age at screening (the time at which they sign the informed consent) with TD.

Methods

Objective(s)

The primary objective of the trial was to compare the efficacy of aripiprazole with placebo in the suppression of tics in children and adolescents (7 to 17 years) with a diagnosis of Tourette's disorder (TD). The primary efficacy measure was change from baseline to endpoint (Week 8) on the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS).

The secondary objective was to evaluate the safety and tolerability of aripiprazole once-weekly (QW) treatment with oral tablets in children and adolescents with a diagnosis of TD. Secondary efficacy measures included Clinical Global Impression Scale for Tourette's Syndrome (CGI-TS) and Gilles de la Tourette Syndrome - Quality of Life Scale (GTS-QOL).

Study design

A phase 3, multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of flexible-dose oral aripiprazole QW tablets in children and adolescents 7 to 17 years of age at screening (the time at which they sign the informed consent) with TD. A total of 126 subjects were planned to be randomly assigned to either aripiprazole QW or placebo QW in a 2:1 ratio (84 subjects in the aripiprazole group and 42 subjects in the placebo group) at approximately 45 sites globally. The trial consisted of 2 distinct phases: a pretreatment phase and a treatment phase. The pretreatment phase consisted of a Screening period, a washout period (when applicable), and a Baseline visit. This was followed by an 8-week treatment phase. There was also a follow-up period (30 ± 3 days) for those subjects who did not roll over into the open-label trial.

The pretreatment phase served the following purposes:

1) To allow for appropriate washout of prohibited medications

2) To ensure subject met inclusion/exclusion criteria

3) To establish a pretreatment baseline of outcome measures

Modifications to a subject's pre-existing treatment were not allowed for the explicit purpose of entering this trial, but could be done only when deemed clinically appropriate by the investigator. Tapering rates for washout medications were at the discretion of the investigator and determined on an individual basis, with consideration to the subject's clinical condition, dose, and known pharmacokinetics (PK) of the medication being tapered, as long as the protocol-mandated discontinuation timeframe was met. The exception was a long-acting depot medication, which could not be tapered and had to be discontinued after the informed consent/assent was obtained. Subjects visited the clinic at Weeks 1, 2, 3, 4, 5, 6, and 8 (± 1 day), at which time the efficacy, safety, and outcome measures were collected. A telephone call to the subject to confirm safety and tolerability was

made at the conclusion of Week 7, when a clinic visit was not required. Subjects who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revision (DSM-IV-TR) diagnostic criteria for TD, as confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (K-SADS-PL), including the Diagnostic Supplement 5 (Substance Abuse and Other Diseases, ie, Tic Disorders), and who had a TTS ≥ 20 on the YGTSS at screening and baseline (randomization) could enter into the trial, once the other inclusion criteria were satisfied and no exclusion criteria had been met. Furthermore, the subject, a designated caregiver, and the investigator had to all agree that the presenting tic symptoms caused impairment in the subject's normal routines, based on academic achievement, occupational functioning, social activities, and/or relationships.

Subjects were randomized to either aripiprazole QW or placebo QW. All subjects randomized to aripiprazole began on a 52.5 mg QW dose on Day 0. At the Week 1 visit, according to the investigator's discretion based on efficacy and tolerability, the dose of aripiprazole could remain at 52.5 mg QW or be increased to 77.5 mg QW. The dose could be increased to 110 mg QW for efficacy as early as Week 2. For the remainder of the trial, the dose could be adjusted up and down among these 3 dose levels, as determined by investigator discretion. General dosing rules included the following:

1) all dose increases should occur at the time of weekly trial visits and 2) all dose increases or decreases had to be incremental, that is, increase to the next higher dose or decrease to the next lower dose.

Study population /Sample size

126 subjects were planned for randomization (84 subjects in the aripiprazole QW group and 42 subjects in the placebo QW group) in this trial from an estimated 45 sites worldwide. A total of 152 unique subjects were screened for the trial and 135 randomized (90 subjects were in the aripiprazole QW group and 45 subjects were in the placebo QW group). The enrollment distribution of randomized subjects across the 6 countries was as follows: United States (42 subjects), Canada (23 subjects), Taiwan (22 subjects), South Korea (17 subjects), Mexico (17 subjects) and Hungary (14 subjects).

This trial enrolled subjects who met the DSM-IV-TR diagnostic criteria for TD, as confirmed by the K-SADS-PL, including the Diagnostic Supplement 5 (Substance Abuse and Other Diseases, ie, Tic Disorders), and who had a TTS ≥ 20 on the YGTSS at screening and baseline (randomization), and met the other inclusion criteria.

Treatments

Subjects were randomised in a 2:1 ratio to receive 8 weeks double-blind treatment with either aripiprazole QW ECER tablets 52.5 mg to 110 mg or matching placebo. QW ECER oral aripiprazole or matching placebo was administered every 7 days beginning on Day 0 of the trial. Doses were to be taken on the same day each week (+-1 day), without regard to meals. Subjects randomised to aripiprazole began on a 52.5 mg QW ECER dose on Day 0. At the Week 1 visit, according to the investigator's discretion based on efficacy and tolerability, the dose of aripiprazole remained at 52.5 mg QW ECER or was increased to 77.5 mg ECER QW. The dose could be increased to 110 mg QW ECERfor efficacy as early as Week 2. For the remainder of the trial, the dose was adjusted up and down among the 3 dose levels, as determined by investigator discretion. General dosing rules included the following: 1) all dose increases should have occurred at the time of weekly trial visits and 2) all dose increases or decreases had to be incremental, that is, increased to the next higher dose or decreased to the next lower dose. Subjects who could not tolerate the lowest titration dose were discontinued from the trial. Of note, according to the protocol, subjects were allowed to discontinue

due to lack of efficacy beginning at Week 5. There was a follow-up period (30 +-3 days) for those subjects who did not roll-over into the open-label trial (Trial 31-10-274). An independent data monitoring committee (IDMC) reviewed and evaluated cumulative safety data collected at regular intervals to ensure the safety of subjects enrolled in the trial.

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline to Week 8 in YGTSS TTS. The key secondary efficacy endpoints were the CGI-TS change score at endpoint (change score obtained from CGI-TS improvement scale assessment) and the mean changes from baseline to endpoint in Gilles de la Tourette - Quality of Life Scale (GTS-QOL) overall score. The other efficacy endpoints were mean change from baseline to endpoint in YGTSS Total score, mean change from baseline to endpoint in Clinical Global Impression Scale for Tourette's Syndrome (CGI-TS) Severity score, response rates (clinical response was defined as > 25% improvement from baseline to endpoint in YGTSS TTS OR a CGI-TS change score of 1 [very much improved] or 2 [much improved] at endpoint) and treatment discontinuation rates.

Statistical Methods

Assuming 5% of the subjects might drop out of the trial without a postbaseline efficacy evaluation, a total of 126 subjects, randomized in a 2:1 ratio (84 subjects to aripiprazole QW and 42 subjects to placebo QW), were needed to provide 85% power at an alpha level of 5% (2-sided) in order to detect a treatment difference of −5 (aripiprazole - placebo) in the primary outcome with a common standard deviation (SD) of 8.5. The difference of −5 was considered a clinically important difference in the treatment of TD. The SD of 8.5 was assumed on the basis of reported treatment effects of oral daily aripiprazole on TD. A trial of oral, once-daily aripiprazole observed an SD of 8.96 for change from baseline in TTS (Otsuka protocol 031-KOA-0703).

The Intention-to-Treat (ITT) Sample was composed of all subjects randomized to double-blind treatment (regardless of whether or not they received treatment). The modified intention-to-treat Sample (mITT) included all subjects randomly assigned to the double-blind treatment, with the exclusion of subjects randomized at sites 002 and 005. These two centers were terminated from conducting this trial due to their failure to abide by Good Clinical Practice Guidelines and the protocol requirements. The mITT Sample was used in place of the ITT sample, which was the primary dataset for all efficacy endpoints, and was analyzed according to the treatment group to which subjects were randomized. The Safety Sample comprised all subjects who were randomized to double-blind treatment and received at least 1 dose of double-blind trial drug. This was the primary dataset for evaluating safety of subjects according to the actual treatments they received.

The primary efficacy analysis was the change from baseline to endpoint (Week 8) in YGTSS TTS. The analysis was performed using a mixed model repeated measures (MMRM) linear model with terms of treatment and visit week as factors, baseline YGTSS TTS as a covariate, and treatment-by-week interactions in the model. Visit week was the time variable for repeated measures. To assess the time trend of treatment effect, statistical analyses were also performed for the change from baseline in YGTSS TTS at each visit.

Key secondary and other efficacy endpoints, in the form of mean change from baseline, were compared between the aripiprazole and placebo groups using a similar method, as described for the primary efficacy analysis. Proportion endpoints, such as response rates and treatment discontinuation rates, were summarized by descriptive statistics (frequency and percent) and compared between the aripiprazole and placebo groups by the Chi-square test.

Sensitivity analyses of the primary endpoint and key secondary endpoint were performed under the assumption that the mechanism of missing data was missing not at random. The type I error of multiple hypothesis testing for the primary and key secondary endpoints was controlled using a p-value based fixed-sequence testing procedure in the order of YGTSS TTS, CGI-TS, and GTS-QOL, ie, one must reject the null hypothesis of an endpoint at the level of 0.05 (2-sided) to test the hypothesis of the subsequent endpoint in the sequence at the level of 0.05 (2-sided).

Safety endpoints were summarized by descriptive statistics using the safety sample.

Results

Recruitment / Number analysed

Of the 135 subjects randomised in the trial, 90 subjects were enrolled in the aripiprazole group and 45 subjects were enrolled in the placebo group. A total of 113 subjects (83.7%) completed the trial, 78 (86.7%) in the aripiprazole group and 35 (77.8%) in the placebo group. Based on the ITT Sample (N = 135), 22 subjects (16.3%) discontinued from the trial, 12 (13.3%) in the aripiprazole group and 10 (22.2%) in the placebo group; 7 subjects (5.2%) discontinued due to an AE, 5 (5.6%) in the aripiprazole group and 2 (4.4%) in the placebo group; 3 subjects (2.2%) discontinued due to withdrawal of consent, 1 (1.1%) in the aripiprazole group and 2 (4.4%) in the placebo group; and 12 (8.9%) subjects discontinued from the trial due to lack of efficacy, 6 (6.7%) in the aripiprazole group and 6 (13.3%) in the placebo group.. Based on the mITT Sample (N = 124), 22 subjects (17.7%) discontinued from the trial, 12 (14.6%) in the aripiprazole group and 10 (23.8%) in the placebo group; 7 subjects (5.6%) discontinued due to an AE, 5 (6.1%) in the aripiprazole group and 2 (4.8%) in the placebo group; 3 subjects (2.4%) discontinued due to withdrawal of consent, 1 in the aripiprazole group (1.2%) and 2 (4.8%) in the placebo group; and 12 subjects (9.7%) discontinued from the trial due to lack of efficacy, 6 (7.3%) in the aripiprazole group and 6 (14.3%) in the placebo group. The number of male and female subjects in the mITT population was balanced, the mean age at trial entry was 11.8 years (range 7 to 17 years) and the majority of subjects were Caucasian (84/124, 67.7%). Overall, the baseline demographic characteristics, including baseline disease status were similar between the aripiprazole and placebo groups for the mITT population. The study protocol allowed patients to withdraw after 5 weeks of placebo-controlled treatment.

Baseline data

The mean age of randomized subjects was 12.0 and 11.5 years in the aripiprazole and placebo groups, respectively. Most subjects were white: 64.6% and 73.8% in the aripiprazole and placebo groups, respectively. The mITT Sample included a higher percentage of males than females in the aripiprazole and placebo groups: 80.5% and 66.7%, respectively, as expected due to the higher incidence of the disease in males. The mean weight and BMI of subjects in the mITT Sample were 51.3 kg and 20.7 kg/m2 and 49.2 kg and 20.7 kg/m2, respectively, in the aripiprazole and placebo groups. The baseline mean total YGTSS of subjects in the mITT Sample was 29.9 and 28.9 in the aripiprazole and placebo groups, respectively.

Efficacy results

Of the 83 subjects randomied in the trial, 20 subjects were enrolled in the aripiprazole 52.5 mg group and 21subjects were enrolled to each of the aripiprazole 77.5 mg, aripiprazole 110 mg and placebo groups. A total of 68 (81.9%) subjects completed the trial. The most frequent reason for discontinuation was sponsor discontinued the trial (6 of 83 [7.2%] subjects). The other main reason for discontinuation from the trial was subject withdrawing consent (4 of 83 [4.8%] subjects). The

mean age of subjects was 11.9 years with a mean time since first diagnosis of 2.7 years. In all treatment groups, slightly more subjects in the 7- to 12-year age group (48 of 83 [57.8%] subjects) were randomised compared to the 13- to 17-year age group (35 of 83 [42.2%] subjects). The mean BMI was 20.0 kg/m2; the mean weight and height were 47.9 kg and 152.4 cm, respectively. The majority of subjects were white (69 of 83 [83.1%] subjects overall) and non-Hispanic or Latino (78 of 83 [94.0%] subjects overall). More black or African American subjects were randomised in the aripiprazole QW ECER 52.5 mg group compared to the other treatment arms.

Since the trial was discontinued by the sponsor with a much smaller sample size than originally planned, no inferential analyses were carried out and instead descriptive statistics were used to summarise all efficacy data, therefore, the data should be interpreted with caution.

Primary endpoint

No meaningful difference in the changes from baseline to Week 8 between treatment groups were was observed in YGTSS TTS in the ITT Sample in the OC and LOCF datasets. The aripiprazole QW ECER 110 mg group showed the largest decrease from baseline. The mean change from baseline in the placebo group was similar to the aripiprazole QW ECER 52.5 mg and 77.5 mg groups.

Secondary endpoints

The CGI-TS change score at Week 8 were was similar between the placebo group and the aripiprazole QW ECER 52.5 mg, and 77.5 mg groups, for the OC and LOCF datasets. No meaningful differences in mean change from baseline were observed in the GTS-QOL Overall Score, for the OC and LOCF datasets; however, the aripiprazole QW ECER 77.5 mg showed the least improvement and the placebo group showed the same improvement as the aripiprazole QW ECER 110 mg group.

Other efficacy endpoints

No meaningful differences in mean change from baseline in the Total YGTSS Score, and CGI-TS Severity Score were observed between treatment groups for the OC and LOCF datasets. The placebo group showed a similar decrease from baseline improvement to the aripiprazole QW ECER 52.5 mg and 77.5 mg groups. The CGI-TS Severity Score showed similar decrease from baseline in all treatment groups.

Safety results

Rates of AEs, SAEs, and Discontinuation of Therapy

90 subjects were exposed to aripiprazole in this trial, receiving an average dose of 75.3 mg QW. In the aripiprazole group, 87.8% (79/90) of subjects were exposed to aripiprazole for > 7 weeks. The overall incidence of TEAEs was 66.7% in the aripiprazole group and 60.0% in the placebo group. Aripiprazole was generally safe and well tolerated by the subjects in this study.

The most frequently reported TEAEs that occurred in the aripiprazole group (with an incidence >=5%) were somnolence (16.7% in the aripiprazole group and 6.7% in the placebo group), headache (13.3% in the aripiprazole group and 4.4%), nausea (13.3% in the aripiprazole group and 8.9%), vomiting (10.0% in the aripiprazole group and 2.2%), fatigue (8.9% in the aripiprazole group and 0%), and increased appetite (6.7% in the aripiprazole group and 2.2%). These TEAEs occurred more frequently in the aripiprazole group than in the placebo group. The most frequently reported TEAE in the placebo group was nasopharyngitis (15.6%), which occurred less frequently in the aripiprazole group (3.3%). Most TEAEs were mild or moderate in intensity. Severe TEAEs reported in the aripiprazole group were dystonia in 2 subjects (2.2%) and the following TEAEs in 1 subject (1.1%) each: ALT increased, AST

increased, blood creatine phosphokinase increased, hyperthermia, musculoskeletal stiffness, tonsillitis, and somnolence. No severe TEAEs were reported in the placebo group.

For the most common TEAEs (with an incidence of ≥ 5% in any aripiprazole group and ≥ 2 times the incidence in the placebo group), the Breslow-Day test of significance for homogeneity was used to assess the odds ratio difference for age, sex, and race subgroups between the aripiprazole and placebo groups. Results of the Breslow-Day Test showed no statistically significant difference between age, sex, or race subgroups for the most common TEAEs for the aripiprazole versus placebo groups. TEAEs considered by the investigator as potentially causally related to the IMP were reported for 40 (44.4%) and 12 (26.7%) subjects in the aripiprazole and placebo groups, respectively. The most frequently reported (experienced by >=5% of subjects in the aripiprazole group) TEAEs considered by the investigator as potentially causally related to the IMP were somnolence (15 subjects [16.7%]), nausea, (12 subjects [13.3%]), fatigue (8 subjects [8.9%]), headache (7 subjects [7.8%]), and increased appetite and vomiting (6 subjects each [6.7%]). In the placebo group, causally related TEAEs reported in more than 1 subject each were nausea (4 subjects [8.9%]) and somnolence (3 subjects [6.7%]). Most TEAEs considered by the investigator as potentially causally related to the IMP were mild or moderate in intensity in both treatment groups. Severe TEAEs considered by the investigator as potentially causally related to the IMP reported in the aripiprazole group were dystonia in 2 subjects (2.2%); ALT increased, AST increased, and blood creatinine phosphokinase increased in 1 subject (1.1%); hyperthermia, musculoskeletal stiffness, and somnolence in 1 subject (1.1%) each. No subjects in the placebo group had severe potentially causally related TEAE.

Serious adverse events were reported for 3 subjects (3.3%) in the aripiprazole group and no subjects in the placebo group. One (1) aripiprazole subject had severe dystonia and severe hyperthermia, both of which were considered by the investigator to be definitely related to the IMP. The second subject had severe dystonia and moderate intensity prolonged QTcB, both of which were considered by the investigator to be probably related to the IMP. The third subject had severe increases in ALT, AST, and creatine phosphokinase (CPK), all of which were considered by the investigator to be probably related to the IMP. In all cases, IMP was discontinued, and the subjects recovered. 5 subjects (5.6%) in the aripiprazole group and 2 subjects (4.4%) in the placebo group discontinued IMP due to TEAEs. The system organ class of investigations had the most subjects with TEAEs leading to discontinuation (3 subjects [3.3%] in the aripiprazole group and 2 subjects [4.4%] in the placebo group). Only 2 TEAEs led to discontinuation of > 1 subject: ECG QT prolonged, which was experienced by 2 subjects in each treatment group, and dystonia, which was experienced by 2 subjects in the aripiprazole group.

No deaths occurred during the trial. No overdose-related TEAEs and no pregnancies were reported during the trial.

With regards to TEAEs of special interest, treatment-emergent AEs related to Extrapyramidal symptoms (EPS) were experienced by 6 subjects (6.7%) in the aripiprazole group and no subjects in the placebo group. The most frequently reported EPS-related TEAE was dystonia (3 subjects [3.3%]), 2 of which were severe and reported as SAEs. Other EPS-related TEAEs reported in the aripiprazole group were muscle spasms, dyskinesia, and tremor in 1 subject (1.1%) each, all of which were of mild intensity. All of the EPS-related TEAEs started during the first 6 days of treatment, except the muscle spasms, which occurred on Day 15.

With regards to Extrapyramidal Symptoms (EPS), The treatment difference between the aripiprazole and placebo groups in the Simpson-Angus Scale (SAS) total score (0.04), Abnormal Involuntary Movement Scale (AIMS) score (-0.32) and Barnes Akathisia Rating Scale (BARS) score ((-0.05) were not statistically significant at Week 8, based on a mixed effect repeated measure model. Similar results were seen for the analyses using the ANCOVA with OC and ANCOVA with LOCF. No post-baseline suicidal behaviour or ideation was observed based on results of reported.

Of the safety rating scales, Swanson, Nolan, and Pelham-IV (SNAP-IV), Children's Yale- Brown Obsessive Compulsive Scale (CY-BOCS), Children's Depression Rating Scale - Revised (CDRS-R), and Paediatric Anxiety Rating Scale (PARS), no statistically significant difference in the change from baseline to Week 8 was observed between the aripiprazole and placebo groups, except on the SNAP-IV, where aripiprazole showed significant improvement over placebo in the hyperactivity/impulsivity average score (p = 0.0328) and the average score of the ADD/ADHD subscale (p = 0.0220).

Laboratory Assessments, Vital Signs, ECG

No mean changes from baseline for any of the serum chemistry laboratory, haematology, or urinalysis tests were considered to be clinically significant. No significant findings were shown in clinical laboratory values, vital signs, physical examinations, and ECG parameters. The mean (+-SD) change from baseline to the last visit in the prolactin test results for the aripiprazole group males (-4.31 [+-5.81] ng/mL) and females (-5.58 [+-7.20] ng/mL) was greater than for the placebo group males (-1.69 [+-8.58] ng/mL) and females (2.06 [+-6.02] ng/mL). No subjects had prolactin values >2 x ULN. These changes are consistent with prolactin data for aripiprazole in other paediatric trials.

Laboratory Measurements of Special Interest

Weight gain-related TEAEs in the aripiprazole and placebo groups were reported for 8 (8.9%) and 1 (2.2%) subjects, respectively. Increased appetite was the most frequently reported weight-gain related TEAE, occurring in 6 (6.7%) subjects in the aripiprazole group and 1 (2.2%) subject in the placebo group. One of these subjects in the aripiprazole group also had a TEAE of weight increased. In addition, in the aripiprazole group, 1 other subject had a TEAE of weight increased (total of 2 subjects [2.2%]) and 1 subject (1.1%) had hyperphagia. All of these events were of mild or moderate intensity and began between Days 1 and 29. As summarised in, the 7 subjects in the aripiprazole group who had a potentially clinically relevant weight gain >=7% at Week 8 had low BMI (< 20 kg/m2) at baseline.

No prolactin-related TEAEs, hyperglycaemia-related or diabetes-related TEAEs were reported during the trial. One subject in the aripiprazole group had a lipid parameterrelated TEAE of mild dyslipidaemia starting on Day 43. No other lipid parameter-related TEAEs were reported during the trial.

31-10-273: A phase 3 multicentre, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of fixed dose QW oral aripiprazole in Children and Adolescents with TD

Description

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of flexible-dose oral aripiprazole QW tablets in children and adolescents 7 to 17 years of age at screening (the time at which they sign the informed consent) with TD.

Methods

Objective(s)

Primary: The primary objective was to compare the efficacy of aripiprazole with placebo in the suppression of tics in children and adolescents (aged 7 to 17 years) with a diagnosis of Tourette's Disorder (TD).

Secondary: The secondary objective was to evaluate the safety and tolerability of aripiprazole once-weekly (QW) treatment with oral tablets in children and adolescents with a diagnosis of TD.

Study design

Trial 31-10-273 was a phase 3, multiple site, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of fixed-dose oral aripiprazole QW tablets in children and adolescents, 7 to 17 years of age at screening (the time at which they signed the informed consent/assent), with TD.

A total of 192 subjects were planned to be randomly assigned to receive one of 3 doses of aripiprazole QW (52.5, 77.5, and 110 mg) or placebo in a 1:1:1:1 ratio (48 subjects each in the aripiprazole QW 52.5, 77.5, and 110 mg groups and 48 subjects in the placebo group) at approximately 55 sites globally. The trial consisted of 2 distinct phases: a pretreatment phase and a treatment phase. The pretreatment phase consisted of a screening period, a washout period (when applicable), and a baseline visit. This was followed by an 8-week treatment phase. There was also a follow-up period (30 +- 3 days) for those subjects who did not roll-over into the open-label trial.

The pretreatment phase served the following purposes:

- To allow for appropriate washout of prohibited medications
- To ensure the subject met the inclusion/exclusion criteria
- To establish a pretreatment baseline of outcome measures

Modifications to a subject's pre-existing treatment were not to be made for the explicit purpose of entering this trial, but were done only when deemed clinically appropriate by the investigator. Tapering rates for washout medications were at the discretion of the investigator and were to be determined on an individual basis, with consideration to the subject's clinical condition, dose, and known pharmacokinetics (PK) of the medication being tapered, as long as the protocol-mandated discontinuation timeframe was met. The exception was a long acting depot medication, which could not have been tapered and would have been discontinued after the informed consent/assent was obtained. All psychotropic medications must have been discontinued for at least 2 weeks (14 days) prior to the baseline visit, with the exception of psychostimulant medications such as methylphenidate (not limited to Concerta®, Metadate CR®, Ritalin LA®, Focalin®, Focalin XR®, Vyvanse®) prescribed for the treatment of symptoms of attention-deficit disorder/attention-deficit hyperactivity disorder (ADD/ADHD), which were permitted during the trial. Use of psychostimulant medications was only permitted if the subject did not develop and/or did not have an exacerbation of the tic disorder after the initiation of treatment with the psychostimulant. In addition, the dose of any psychostimulant must have been stable for at least 4 weeks prior to screening. All selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors must have been discontinued at least 4 weeks (28 days) prior to the baseline visit. In addition, long-acting (depot) neuroleptics must have been discontinued for at least one full cycle plus 2 weeks prior to the baseline visit. Clonidine, guanfacine, guanabenz, atomoxetine, and carbamazepine were prohibited during the trial and must have been discontinued for at least 2 weeks prior to baseline. Subjects must have discontinued aripiprazole treatment at least 30 days prior to the screening visit. Subjects not in need of medication washout proceeded to the trial baseline visit after the inclusion/exclusion criteria were met.

Subjects visited the clinic at Weeks 1, 2, 3, 4, 5, 6, and 8 (+- 1 day), at which time efficacy, safety, and outcome measures were collected. A telephone call to the subject to confirm safety and tolerability was made at the conclusion of Week 7, when the clinic visit was not scheduled. Subjects who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revision (DSM-IV-TR)

diagnostic criteria for TD, as confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (K-SADS-PL), including the Diagnostic Supplement 5 (Substance Abuse and Other Diseases, ie, Tic Disorders), and who had a Total Tic Score (TTS) >= 20 on the Yale Global Tic Severity Scale (YGTSS) at screening and baseline (randomization), could have entered into the trial once the other inclusion criteria were satisfied and no exclusion criteria were met. Furthermore, the subject, a designated caregiver, and the investigator must have all agreed that the presenting tic symptoms caused impairment in the subject's normal routines, based on academic achievement, occupational functioning, social activities, and/or relationships. Subjects were randomized to receive either aripiprazole or placebo. All subjects randomized to one of the 3 aripiprazole treatment groups began a 52.5-mg dose on Day 0 with the dose titrated to achieve the randomized dose at Day 0 for the 52.5 mg group, Week 1 for the 77.5 mg group, and Week 2 for the 110 mg group. Once subjects reached the randomized dose, they were to remain on the randomized dose for the duration of the treatment period. The titration schedule must have been adhered to with no dose decreases allowed at any time. Subjects not tolerating any dose were to be discontinued from the trial.

Study population /Sample size

A total of 192 subjects were planned to be randomly assigned in the trial. Overall, 83 subjects were randomized in the trial and treated: 20 subjects in the aripiprazole QW 52.5 mg group, 21 subjects in the aripiprazole QW 77.5 mg group, 21 subjects in the aripiprazole QW 110 mg group, and 21 subjects in the placebo group. A total of 68 subjects completed the trial: 17 subjects in the aripiprazole QW 52.5 mg group, 17 subjects in the aripiprazole QW 77.5 mg group, 16 subjects in the aripiprazole QW 110 mg group, and 18 subjects in the placebo group. A total of 83 subjects were analyzed for safety and efficacy.

The key inclusion criteria were as follows:

1) The subject was a male or female child or adolescent, 7 to 17 years of age (inclusive) at the time of signing the informed consent/assent.

2) The subject met current DSM-IV-TR diagnostic criteria for TD, as confirmed by the K-SADS-PL, including the Diagnostic Supplement 5 (Substance Abuse and Other Diseases, ie, Tic Disorders).

3) The subject had a TTS >= 20 on the YGTSS at screening and baseline (randomization).

4) The subject, a caregiver, and the investigator all agreed that the presenting tic symptoms caused impairment in the subject's normal routines, which included academic achievement, occupational functioning, social activities, and/or relationships.

Treatments

Subjects were randomised in a 1:1:1:1 ratio to receive 8 weeks double-blind treatment with one of the 3 doses of QW ECER aripiprazole (52.5 mg, 77.5 or 110 mg) or a matching placebo. QW oral aripiprazole or matching placebo was administered every 7 days beginning on Day 0 of the trial. Doses were taken on the same day each week (+-1 day), without regard to meals. All subjects' randomised to one of the 3 aripiprazole treatment groups began on a 52.5-mg dose on Day 0 with the dose titrated to achieve the randomized dose at Day 0 for the 52.5 mg group, Week 1 for the 77.5 mg group, and Week 2 for the 110 mg group. Once the subject reached the randomised dose, they remained on this dose for the duration of the treatment period. The titration schedule was adhered to with no dose decreases allowed at any time. Subjects not tolerating any dose were discontinued. There was a

follow-up period (30 +- 3 days) for those subjects who did not roll-over into the open-label trial (Trial 31-10-274).

Outcomes/endpoints

Efficacy: The primary efficacy endpoint was the change from baseline to endpoint (Week 8) in YGTSS TTS.

The key secondary endpoints included the following:

- Mean CGI-TS Change score at endpoint (change score obtained from CGI-TS improvement scale assessment)
- Mean changes from baseline to endpoint in GTS-QOL overall score

The other efficacy endpoints included:

- Mean change from baseline to endpoint in Total YGTSS score
- Mean change from baseline to endpoint in CGI-TS Severity score
- Response rates (clinical response was defined as a > 25% improvement from baseline to endpoint in YGTSS TTS OR a CGI-TS Change score of 1 [very much improved] or 2 [much improved] at endpoint)
- Treatment discontinuation rates

Pharmacokinetics/pharmacodynamics: Blood samples were collected during Weeks 6 and 8 and plasma concentrations of aripiprazole and its metabolite, dehydro-aripiprazole, were assessed. If possible, exploratory population and PK/pharmacodynamic modeling was to be performed.

Safety: Safety endpoints included the following:

- AEs
- Laboratory tests (hematology, serum chemistry [including prolactin, glycosylated hemoglobin, and TSH], urinalysis, and pregnancy tests)
- Vital signs
- ECGs
- AIMS
- BARS
- SAS
- C-SSRS
- ADD/ADHD Subscale of SNAP-IV
- CY-BOCS
- CDRS-R
- PARS
- Body weight
- Waist circumference

- BMI

Pharmacokinetic/pharmacodynamic/pharmacogenomics

Plasma concentrations of aripiprazole and its metabolite, dehydro-aripiprazole, were quantitated using a validated high-performance liquid chromatography with tandem mass spectrometry method. Blood samples were collected during the Week 6 and Week 8/Early Termination visits, at the same time when safety laboratory samples were collected. Plasma concentrations of aripiprazole and its metabolite, dehydro-aripiprazole, were reported and summarized using descriptive statistics. Results of pharmacogenomic testing to assess cytochrome P450 2D6 metabolizer status were also reported. Plasma concentration data were further analyzed as part of a population PK analysis and PK/pharmacodynamic (PD) modeling and reported separately.

Statistical Methods

Subject Samples: The Intent-to-treat (ITT) Sample, which included all subjects randomly assigned to the double-blind treatment, was the primary dataset for all efficacy endpoints and was analyzed according to the treatment group to which subjects were randomized. The Safety Sample included all subjects who were randomized to double-blind treatment and received at least 1 dose of the investigational medicinal product (IMP). The Safety Sample was analyzed according to the treatment received. If a subject randomized to placebo ever took an active aripiprazole dose, the subject was analyzed according to the highest aripiprazole dose he or she received. The Observed Case (OC) dataset for the ITT Sample and Safety Sample at the endpoint or at a particular trial week consisted of data from subjects in the corresponding sample who had non-missing scores for the efficacy or safety variable under analysis at that week.

Efficacy: Since the actual trial was discontinued by the sponsor, with a much smaller sample size than originally planned, changes were made to the efficacy analyses that were pre-specified in the protocol. No inferential analyses were carried out and instead descriptive statistics were used to summarize efficacy data of this trial.

Safety: In addition to the analysis of standard safety parameters, physical examination findings, weight, height, BMI, waist circumference, EPS, ADD/ADHD subscale of SNAP-IV, CY-BOCS, CDRS-R, PARS, and suicidality (C-SSRS) were evaluated through analysis of data from appropriate scales. Safety variables were summarized by incidence rates and their changes from baseline, as appropriate. In general, summary statistics of changes from baseline were provided for safety variables based on all available data (ie, OC dataset) for each postbaseline visit and for the last visit. Data from unscheduled visits were used in the mean change from baseline calculations and incidence calculations.

Results

Recruitment/ Number analysed

A total of 105 unique subjects were screened and 83 subjects were randomized: Of the 83 subjects randomied in the trial, 20 subjects were enrolled in the aripiprazole 52.5 mg group and 21subjects were enrolled to each of the aripiprazole 77.5 mg, aripiprazole 110 mg and placebo groups. A total of 68 (81.9%) subjects completed the trial. The most frequent reason for discontinuation was sponsor discontinued the trial (6 of 83 [7.2%] subjects). The other main reason for discontinuation from the trial was subject withdrawing consent (4 of 83 [4.8%] subjects). The mean age of subjects was 11.9 years with a mean time since first diagnosis of 2.7 years. In all treatment groups, slightly more subjects in the 7- to 12-year age group (48 of 83 [57.8%] subjects) were randomised compared to the 13- to 17-year age group (35 of 83 [42.2%] subjects). The mean BMI was 20.0 kg/m2; the mean

weight and height were 47.9 kg and 152.4 cm, respectively. The majority of subjects were white (69 of 83 [83.1%] subjects overall) and non-Hispanic or Latino (78 of 83 [94.0%] subjects overall). More black or African American subjects were randomised in the aripiprazole QW ECER 52.5 mg group compared to the other treatment arms.

Baseline data

The trial was terminated early based on the review of the recent data from placebo-controlled Trial 31-10-272 (aripiprazole QW) relative to the results of the placebo-controlled Trial 31-12-293 (aripiprazole once daily [QD]) in subjects with TD. The aripiprazole QW formulation was found to be statistically superior to placebo in Trial 31-10-272, but the demonstrated efficacy was not as robust as that observed with the QD formulation. Therefore, the QW formulation will not be pursued for the treatment of TD. Importantly, the trial closure was unrelated to any safety issues (no signals or items of concern have been identified).

The mean age of subjects was 11.9 years with a mean time since first diagnosis of 2.7 years. The majority of subjects were white (69 of 83 [83.1%] subjects overall) and non-Hispanic or Latino (78 of 83 [94.0%] subjects overall).

Efficacy results

As the actual randomized population was much smaller than the planned size, efficacy was analyzed using descriptive statistics only; therefore, data should be interpreted with caution. No meaningful differences in the change from baseline to Week 8 between treatment groups was observed in YGTSS TTS in the ITT Sample in the OC and last observation carried forward (LOCF) datasets.

Change score at Week 8 was similar between the placebo group and the aripiprazole QW 52.5 mg and 77.5 mg groups, for the OC and LOCF datasets. The change score was the lowest in the aripiprazole QW 110 mg group. No meaningful differences in in mean change from baseline were observed in the GTS-QOL Overall Score, Total YGTSS Score, and CGI-TS Severity Score for the OC and LOCF datasets. The highest rate of responders was the aripiprazole QW 110 mg group for both the OC and LOCF datasets (13 responders [81.3%] and 15 responders [75.0%], respectively). A total of 15 of 83 (18.1%) subjects discontinued the trial. Of the 15 subjects who discontinued from the trial, 9 subjects discontinued for reasons other than sponsor discontinued the trial. The highest instance of treatment discontinuation for reasons other than sponsor discontinued the trial was seen in the aripiprazole QW 52.5 mg and QW 110 mg groups (3 of 20 [15.0%] subjects and 3 of 21 [14.3%] subjects, respectively) and lowest incidence was seen in the placebo group (1 of 21 [4.8%] subjects.

Pharmacokinetic/pharmacodynamic/pharmacogenomics Results: The PK samples collected in this trial were analyzed for aripiprazole and dehydro-aripiprazole concentrations and results are reported in the bioanalytical report. No further analysis or data summaries were conducted or planned for this trial.

Safety results

The aripiprazole QW 110 mg group reported the highest incidence of subjects with treatment-emergent adverse events (TEAEs) (17 of 21 [81.0%] subjects reported 57 TEAEs). Similar incidences of TEAEs were reported in the aripiprazole QW 52.5 mg, aripiprazole QW 77.5 mg, and placebo groups. Most TEAEs were mild or moderate in severity. No severe TEAEs were reported in the placebo group whereas there were 2 severe TEAEs reported in the aripiprazole QW 77.5 mg group, and 1 severe TEAE reported each in the aripiprazole QW 52.5 mg and aripiprazole QW 110 mg groups. Only 1 subject discontinued from the trial due to AEs; this subject was in the aripiprazole QW 77.5 mg group. Fewer

subjects in the placebo group reported TEAEs potentially causally related to IMP than in the aripiprazole groups.

No deaths or serious TEAEs were reported during the trial. EPS-related TEAEs were reported for 3 subjects (tremor was reported in 1 of 20 [5.0%] subjects in the aripiprazole QW 52.5 mg group, muscle spasm in 1 of 21 [4.8%] subjects in the aripiprazole QW 110 mg group, and akathisia in 1 of 21 [4.8%] subjects in the placebo group). Increased weight was reported by 1 of 20 (5.0%) subjects in the aripiprazole QW 52.5 mg group and 1 of 21 (4.8%) subjects in the aripiprazole QW 110 mg group. Increased appetite was reported in 1 of 21 (4.8%) subjects in the aripiprazole QW 77.5 mg group. A prolactin-related TEAE of decreased blood prolactin was reported for 1 of 20 (5.0%) subjects in the aripiprazole QW 52.5 mg group. No suicide-, hyperglycemia-, diabetes-, lipid parameter-, or overdose-related AEs were reported during the trial. No other meaningful findings were shown in clinical laboratory values, vital signs, physical examinations, or ECG parameters.

No meaningful differences in change from baseline were observed in the AIMS, BARS, SAS, C-SSRS, ADD/ADHD Subscale of SNAP-IV, CY-BOCS, CDRS-R, or PARS between treatment groups.

31-10-274: A phase 3 open-label, multicentre study, to evaluate the long-term safety and tolerability of QW oral aripiprazole in children and adolescents with TD

Description

Trial 31-10-274 was a 52-week open-label, multicentre safety investigation of 52.5 mg, 77.5 mg, and 110 mg QW ECER aripiprazole in children and adolescents with a diagnosis of TD. Subjects who successfully completed either of the randomised, doubleblind, placebo-controlled trials (Trials 31-10-272 or 31-10-273) were eligible to enter this extension trial, provided that continuation of treatment was clinically warranted, as judged by the investigator, and there were no significant protocol deviations or clinically relevant AEs precluding inclusion in the trial. Prior to Protocol Amendment 2, subjects who completed Week 5 in the parent trial and were terminated early due to lack of efficacy were also eligible to enter this trial. At the Week 7 (+-1 day) visit of the doubleblind trials, subjects took their final dose of double-blind trial medication. On Day 0 of the open-label trial, subjects began taking the open-label QW ECER aripiprazole treatment.

Methods

Objective(s)

Primary: The primary objective was to evaluate the long-term safety and tolerability of aripiprazole once-weekly (QW) treatment with oral tablets in children and adolescents (7 to 17 years) with a diagnosis of Tourette's disorder (TD).

Secondary: The secondary objectives were:

To evaluate the efficacy of QW aripiprazole in the suppression of tics in children and adolescents with a diagnosis of TD, as measured by change from baseline to endpoint on the Total Tic score (TTS) of the Yale Global Tic Severity Scale (YGTSS);

To evaluate the long-term effect of QW aripiprazole flexibly dosed on health-related quality of life in children and adolescents with a diagnosis of TD, as measured by the Gilles de la Tourette Syndrome-Quality of Life Scale (GTS-QOL).

Study design

Subjects who successfully completed either of the randomised, doubleblind, placebo-controlled trials (Trials 31-10-272 or 31-10-273) were eligible to enter this extension trial, provided that continuation of treatment was clinically warranted, as judged by the investigator, and there were no significant protocol deviations or clinically relevant AEs precluding inclusion in the trial. All subjects entering trial 31-10-274 were assigned to QW ECER aripiprazole, which was flexibly dosed QW at the discretion of the investigator on the basis of treatment response and medication tolerability. All subjects began on a 52.5-mg dose. At the Week 1 visit, according to the investigator's discretion based on efficacy and tolerability, the dose of aripiprazole remained at 52.5 mg or was increased to 77.5 mg. The dose was further increased to 110 mg for efficacy needs as early as Week 2. For the remainder of the trial, the dose was adjusted between the 3 dose levels, at the investigator's discretion. General dosing rules included all dosing changes should have been made at a scheduled visit, however, if a dosing change was made prior to a visit, there must have been one week between dose changes; all dose increases or decreases must have been incremental; that is, increased to the next higher dose or decreased to the next lower dose

Study population /Sample size

Approximately 223 children and adolescent subjects with TD were expected to be eligible to rollover from Trials 31-10-272 and 31-10-273. Approximately 156 subjects were expected to be eligible and consent to continue in this open-label extension trial. A total of 170 subjects were actually enrolled in this trial (114 subjects from Trial 31-10-272 and 56 subjects from Trial 31-10-273) and received at least one dose of trial medication. Overall, 170 subjects were included in the safety population and 168 subjects were analyzed for efficacy; 2 subjects, who discontinued early, had no postbaseline efficacy assessment and, therefore, were not included in the efficacy analysis.

Subjects must have successfully

completed the final assessment visit or, prior to Protocol Amendment 2, discontinued

because of lack of efficacy at Week 5 or later in either Trial 31-10-272 or Trial 31-10-273 and completed all required assessments for the Week 8/early termination visit to be

eligible to rollover into this open-label trial.

Treatments

All subjects who qualified for the trial were assigned to treatment with open-label aripiprazole QW as a flexible-dose regimen. Once-weekly aripiprazole was administered every 7 days, beginning on Day 0 (Baseline) of the open-label trial. Doses were to be taken on the same day each week (+- 1 day) without regard to meals. The open-label treatment period was 52 weeks. Three enteric-coated extended-release (ECER) dose strengths of an aripiprazole tablet formulation were used in this trial: The route of administration was oral. Aripiprazole tablets were manufactured by Patheon Pharmaceuticals (US). The lot numbers of trial medication were as follows:

- Aripiprazole ECER 52.5-mg tablet: lots 3089002R and 3097022R
- Aripiprazole ECER 77.5-mg tablet: lots 3089003R and 3097023R
- Aripiprazole ECER 110-mg tablet: lots 3089004R and 3097024R

As a general rule, the maintenance dose of trial medication was at the discretion of the investigator and depended on the subject's clinical response and medication tolerability. All subjects began on a

52.5-mg dose QW. At Week 1, according to the investigator's discretion based on efficacy and tolerability, the dose of aripiprazole QW could have remained at 52.5 mg or been increased to 77.5 mg. The dose could have been increased to 110 mg QW for efficacy needs as early as Week 2. For the remainder of the trial, the dose could have been adjusted between these 3 dose levels, as determined by investigator discretion. General dosing rules included the following:

1) All dosing changes were to be made at a scheduled visit; however, if the dose change was made prior to a visit, there must have been one week between dose changes.

2) All dose increases or decreases must have been incremental; that is, increased to the next higher dose or decreased to the next lower dose.

The open-label treatment period was planned to be 52 weeks. Because the trial was terminated early, not all subjects were permitted to complete 52 weeks of aripiprazole QW.

Outcomes/endpoints

Safety (Primary Endpoint): The safety endpoints included assessment of the following:

- AEs
- Laboratory tests (hematology, serum chemistry [including prolactin and thyroid-stimulating hormone], urinalysis, and pregnancy tests)
- Vital signs
- ECGs
- AIMS and other EPS scales
- C-SSRS
- ADD/ADHD Subscale of SNAP-IV
- CY-BOCS
- CDRS-R
- PARS
- Body weight
- Waist circumference
- BMI

Efficacy (Secondary Endpoint): The secondary efficacy endpoints assessed included the following:

- Change from baseline to endpoint in YGTSS TTS
- Mean CGI-TS Change score at endpoint (Change score obtained from CGI-TS improvement scale assessment)
- Mean change from baseline to endpoint in Total YGTSS score
- Response rates (clinical response was defined as a > 25% improvement from baseline to endpoint in YGTSS TTS, OR a CGI-TS Change score of 1 [very much improved] or 2 [much improved] at endpoint)
- Treatment discontinuation rates

Functional outcome (Secondary Endpoint): The functional outcome endpoint (considered a secondary endpoint) was the mean change from baseline to endpoint in GTS-QOL overall score.

Statistical Methods

There was no formal sample size calculation to achieve a target power; approximately 223 children and adolescent subjects with TD were expected to be eligible to rollover into this trial.

Subject Samples: The Safety Sample included all subjects who received at least one dose of open-label trial medication. The Efficacy Sample included all subjects who received at least one dose of open-label trial medication, and had a baseline and at least one postbaseline efficacy evaluation. The Safety Sample was used for all statistical summaries for safety endpoints and the Efficacy Sample was used for efficacy endpoints, unless otherwise specified. The Observed Case dataset for the Safety Sample or Efficacy Sample at the endpoint or at a particular trial week consisted of data from all subjects who had nonmissing scores at that week for the safety or efficacy variable under analysis.

Efficacy: No inferential statistical analyses were planned for this open-label trial and descriptive statistics are provided for all efficacy variables. Continuous variables were summarized by tabulations of mean, median, range, and standard deviation. Tabulations of frequency and percentage were provided for categorical variables. The efficacy variables, which included YGTSS TTS and Total YGTSS score, were summarized by change from baseline to endpoint and also by change over time. The functional outcome variable, GTS-QOL, was summarized by change from baseline to endpoint and also by change over time. Efficacy measured by CGI-TS Change score or response rates was summarized for those evaluations at each visit.

Safety: Safety variables were summarized by descriptive statistics. The incidences of suicidality, suicidal behavior, and suicidal ideation were calculated from the potential suicide events recorded on the C-SSRS forms, and the results were summarized by visit.

Results

Recruitment/ Number analysed

114 subjects were enrolled from Trial 31-10-272 and 56 subjects were enrolled from Trial 31-10-273. A total of 89 (52.4%) subjects completed the trial: 60 (52.6%) subjects from Trial 31-10-272 and 29 (51.8%) subjects from Trial 31-10-273. The most frequent reason for trial discontinuation was the sponsor discontinued the trial (43 of 170 [25.3%] subjects). Other main reasons for discontinuations included: subject withdrew consent (12 [7.1%] subjects) and subject met withdrawal criteria (10 [5.9%] subjects).

Baseline data

A total of 170 subjects were screened for this trial and enrolled: 114 subjects were enrolled from Trial 31-10-272 and 56 subjects were enrolled from Trial 31-10-273. Overall, 170 subjects were included in the safety population and 168 subjects were analyzed for efficacy. A total of 89 (52.4%) subjects completed the trial (ie, completed the Week 52 Visit). The most frequent reason for trial discontinuation was the sponsor discontinued the trial (43 of 170 [25.3%] subjects). Other main reasons for discontinuations included subject withdrew consent (12 [7.1%] subjects) and subject met withdrawal criteria (10 [5.9%] subjects).

This trial was discontinued early based on the review of the recent data from placebo-controlled Trial 31-10-272 (aripiprazole QW) relative to the results of placebo-controlled Trial 31-12-293 (aripiprazole

once daily [QD]) in subjects with TD. The aripiprazole QW formulation was found to be statistically superior to placebo in Trial 31-10-272, but the demonstrated efficacy was not as robust as that observed with the QD formulation in Trial 31-12-293. Therefore, the QW formulation will not be pursued for the treatment of TD. Importantly, the trial closure was unrelated to any safety issues (no signals or items of concern have been identified).

The mean age of subjects was 12.2 years with a mean time since first diagnosis of 2.3 years. Subjects were evenly distributed between age groups: 89 of 170 (52.4%) subjects in the 7- to 12-year age group and 81 of 170 (47.6%) subjects in the 13- to 18-year age group (subjects who turned 18 during the parent trial were permitted to enroll in this trial). The mean weight and BMI were 51.5 kg and 21.0 kg/m2, respectively. The majority of subjects were White (117 of 170 [68.8%] subjects) and not Hispanic or Latino (136 of 170 [80.0%] subjects).

Efficacy results

No primary efficacy endpoints were included.

Secondary efficacy endpoints

Since the trial was discontinued by the sponsor, no inferential analyses were carried out and only descriptive statistics were used to summarize all efficacy data, therefore, data should be interpreted with caution. The response rate based on the OC data ranged from 66.2% to 80.8% during the course of the trial. At the last visit, 117 of 170 (71.3%) subjects were responders. Overall, 81 of 170 (47.6%) subjects discontinued the trial; the primary reason for discontinuation was the sponsor discontinued the trial. Only 38 of 170 (22.4%) subjects discontinued the trial for reasons other than sponsor discontinued trial.

As expected, no clinically meaningful differences were observed in CGI-TS Change score, CGI-TS Severity of Illness score, or the change from baseline in YGTSS TTS, Total YGTSS score, or GTS-QOL overall score; subjects rolled over from another trial and those who were on aripiprazole in the parent trial already improved in the previous trial. The majority of subjects (66.2% to 80.8%) responded to treatment with the aripiprazole QW formulation during the course of the trial. Overall, 81 of 170 (47.6%) subjects discontinued treatment, primarily because the sponsor discontinued the trial. Only 38 of 170 (22.4%) subjects discontinued treatment for reasons other than the sponsor discontinued the trial.

Safety results

No deaths occurred during the trial. Serious treatment-emergent AEs (TEAEs) were reported for 5 of 170 (2.9%) subjects. The serious TEAEs consisted of TD (worsening Tourette's syndrome) in one subject; appendicitis and suicidal ideation in one subject; type 1 diabetes mellitus in one subject; tremor in one subject; and increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood creatine phosphokinase (CPK), and increased blood lactate dehydrogenase (LDH) in one subject. All of the serious TEAEs were reported for subjects who rolled over from Trial 31-10-272. Only the serious TEAEs of increased ALT, increased AST, increased blood CPK, and increased blood LDH were considered by the investigator to be potentially related to investigational medicinal product (IMP); these events resolved. Treatment-emergent AEs that led to IMP discontinuation were reported for 6 of 170 (3.5%) subjects. The TEAEs leading to discontinuation of IMP included depressed mood, intentional self-injury, nausea, tonsillitis, tremor, and type 1 diabetes mellitus, which were reported for one subject each. All of the TEAEs that led to discontinuation of IMP were reported for subjects who rolled over from Trial 31-10-272. The only TEAE that led to the

discontinuation of IMP and was considered by the investigator as potentially causally related to IMP was nausea, which was moderate in severity and resolved.

Overall Incidence of Adverse Events by Parent Trial (Safety Sample)			
Number of Subjects	**31-10-272[a] (N=114) n (%)[b]**	**31-10-273[a] (N=56) n (%)[b]**	**Total (N=170) n (%)[b]**
Death	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE	5 (4.4)	0 (0.0)	5 (2.9)
Discontinuation due to TEAE	6 (5.3)	0 (0.0)	6 (3.5)
Any TEAE	75 (65.8)	29 (51.8)	104 (61.2)

[a]Subjects who rolled over from the respective parent trial into this trial.

[b]Percentages are based on the number of treated subjects.

The most frequently reported TEAEs (with ≥ 5% incidence) were headache (11.2%), increased weight (8.2%), nasopharyngitis, upper respiratory tract infection, and vomiting (7.1% each), somnolence (6.5%), and nausea (5.9%). Treatment-emergent AEs related to EPS were experienced by 8 subjects. No meaningful changes were observed for the EPS rating scales of AIMS, SAS, and BARS. Suicide-related TEAEs were reported for 3 subjects and consisted of suicidal ideation and intentional self-injury; none of these were considered by the investigator to be potentially causally related to IMP. Suicidality and suicidal ideation were each reported on the C-SSRS for 4 of 169 (2.4%) subjects and emergence of suicidal ideation was reported on the C-SSRS for 3 of 167 (1.8%) subjects.

Weight gain-related TEAEs were reported for 15 subjects; of those, increased weight was reported for 14 of 170 (8.2%) subjects and increased appetite was reported for 4 of 170 (2.4%) subjects. Two of 170 (1.2%) subjects had prolactin-related TEAEs of decreased blood prolactin, 1 of 170 (0.6%) subjects had a hyperglycemia- and diabetes-related TEAE of type 1 diabetes mellitus, and 1 of 170 (0.6%) subjects had a lipid parameter-related TEAE of dyslipidemia; no subjects had TEAEs related to overdose.

Overall, 82 of 166 (49.4%) subjects had a potentially clinically relevant weight gain (> 7%) during the trial; however, the majority of these appear to be due to the normal growth of this pediatric population. Overall, the mean (range) change from baseline to last visit in weight and BMI were 3.8 (−15.3 to 21.2) kg and 0.6 (−5.8 to 6.8) kg/m2, respectively.

Elevated fasting triglycerides was the most frequently reported laboratory value of potential clinical relevance (19 of 145 [13.1%] subjects); however, 11 of these subjects had elevated fasting triglyceride levels at baseline for the parent trial and/or this trial. No other meaningful findings were shown in clinical laboratory values, vital signs, physical examinations, or ECG parameters.

Of the safety rating scales, SNAP-IV, CY-BOCS, CDRS-R, and PARS, no clinically meaningful differences in the changes from baseline to last visit were observed.

2.2.3. Discussion on clinical aspects

Study 31-10-272

Aripiprazole was efficacious in the treatment of tics in children and adolescents (aged 7 to 17 years) with a diagnosis of TD. The improvement after administration of oral weekly doses of 52.5 to 110 mg of aripiprazole (average dose of 75.3 mg QW) in the primary efficacy endpoint of YGTSS TTS was observed at Week 8. Efficacy was supported by statistically significant changes in the key secondary endpoint of CGI-TS Change Score. Oral doses of 52.5 mg QW to 110 mg QW of aripiprazole (average

dose of 75.3 mg QW) were generally well tolerated in pediatric subjects with TD, and no new safety findings were identified in this population.

Unfortunately these results were worse than the ones performed on TD patients with the standard formulation. As such, the formulation was abandoned, and studies 273 and 274 were discontinued.

Study 31-10-273

This trial was terminated early; however, this was not due to any safety issue. Since the trial was terminated early, no inferential analyses were carried out and instead descriptive statistics were used to summarize efficacy data of this trial.

The aripiprazole QW 110 mg group reported the highest incidence of subjects with TEAEs (17 of 21 [81.0%] subjects reported 57 TEAEs). Similar incidences of TEAEs were reported in the aripiprazole QW 52.5 mg, aripiprazole QW 77.5 mg, and placebo groups. Most TEAEs were mild or moderate in severity. No deaths or serious TEAEs were reported during the trial. Only 1 subject discontinued from the trial due to AEs; this subject was in the aripiprazole QW 77.5 mg group. Treatment-emergent AEs potentially causally related to IMP were reported for fewer subjects in the placebo group than the aripiprazole groups. EPS-related TEAEs were reported for 3 subjects (tremor was reported in 1 of 20 [5.0%] subjects in the aripiprazole QW 52.5 mg group, muscle spasms in 1 of 21 [4.8%] subjects in the aripiprazole QW 110 mg group, and akathisia in 1 of 21 [4.8%] subjects in the placebo group).

Increased weight was reported for 1 of 20 (5.0%) subjects in the aripiprazole QW 52.5 mg group and 1 of 21 (4.8%) subjects in the aripiprazole QW 110 mg group. Increased appetite was reported in 1 of 21 (4.8%) subjects in the aripiprazole QW 77.5 mg group. A prolactin-related TEAE (decreased blood prolactin) was reported for 1 of 20 (5.0%) subjects in the aripiprazole QW 52.5 mg group. No suicide-, hyperglycemia-, diabetes-, lipid parameter-, or overdose-related AEs were reported during the trial. No other meaningful differences were shown in clinical laboratory values, vital signs, physical examinations, or ECG parameters. No meaningful differences in change from baseline were observed in the AIMS, BARS, SAS, C-SSRS, ADD/ADHD Subscale of SNAP-IV, CY-BOCS, CDRS-R, or PARS between treatment groups. No meaningful differences in the change from baseline to Week 8 between treatment groups were observed in YGTSS TTS in the ITT Sample in the OC and LOCF datasets. The CGI-TS change scores at Week 8 were similar between the placebo group and the aripiprazole QW 52.5 mg and 77.5 mg groups, for the OC and LOCF datasets. No meaningful differences in mean change from baseline were observed between treatment groups in the GTS-QOL Overall Score, Total YGTSS Score, and CGI-TS Severity Score for the OC and LOCF datasets. The highest rate of responders was the aripiprazole QW 110 mg group for both the OC and LOCF datasets (13 responders [81.3%] and 15 responders [75.0%], respectively).

Study 31-10-274

Long-term treatment (up to one year) with oral aripiprazole 52.5 to 110 mg QW was rather well tolerated in pediatric subjects with TD. The most frequently reported TEAEs (with $\geq$ 5% incidence) after treatment with aripiprazole QW (headache, increased weight, nasopharyngitis, upper respiratory tract infection, vomiting, somnolence, and nausea) were consistent with the known safety profile of aripiprazole, with the exception of upper respiratory tract infection. Serious TEAEs considered to be potentially related to IMP were reported for 1 subject and included increased ALT, increased AST, increased blood CPK, and increased blood LDH. Only 1 TEAE leading to the discontinuation of IMP was considered potentially related to IMP (nausea). The most frequently reported potentially clinically relevant abnormalities included weight gain (>7%) (49.4%) and elevated fasting triglycerides (13.1%); most of the weight gain observed during this trial appears to be due to normal growth in this pediatric population. No other meaningful findings were shown in clinical laboratory values, vital signs, physical examinations, and ECG parameters. No meaningful changes were observed for the EPS rating

scales (AIMS, SAS, and BARS), SNAP-IV, CY-BOCS, CDRS-R, or PARS. Suicide-related TEAEs were reported for 3 subjects; none of these were considered potentially related to IMP. In addition, suicidality (2.4%), suicidal ideation (2.4%), and emergence of suicidal ideation (1.8%) were reported on the C-SSRS.

As expected no clinically meaningful changes from baseline were observed for the efficacy scales; subjects rolled over from another trial and those who were on aripiprazole in the parent trial already improved in the previous trial. However, the majority of subjects (66.2% to 80.8%) responded to treatment with aripiprazole QW during the course of the trial. This trial was terminated early; however, this was not due to any safety issue.

Nevertheless, the number of patients with weight gain was relevant, 82 of 166 (49.4%) subjects had a potentially clinically relevant weight gain (> 7%) during the trial. It hardly should be due to normal child and adolescent growth, as some of the growing children would not increase >7% their weight.

3. CHMP's overall conclusion and recommendation

Overall conclusion

These studies were performed in TD patients, within the plan for the development of a new once a week aripiprazole formulation. The efficacy results lagged behind the once a day marketed formulation studies 31-12-293 and 031-KOA-0703) . Safety results: Adverse events were in the range of adverse events on the above mentioned studies performed with the standard formulation, both in frequency, intensity and severity, considering the short duration of 31-10-272, and the abruptly ended 31-10-273 and 31-10-274. Even weight gain, an adverse event that is time dependent, was rather different from 31-12-293 / 031-KOA-0703, but in line with the weight gain observed on long term treatment of children in other indications. As such, the presented data is not adding useful information to what is already known with aripiprazole. No update on SmPC or PL is suggested.

Submission was accompanied with the information that the MAH would not apply to a change in SmPC.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.