



## Clinical trial results:

### A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2012-003488-23                |
| Trial protocol           | HU FI BE SE ES GB IT DE NL BG |
| Global end of trial date | 03 September 2013             |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 02 March 2016  |
| First version publication date | 06 August 2015 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | 31-12-293 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01727700 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Otsuka Pharmaceutical Development & Commercialization, Inc.  |
| Sponsor organisation address | 2440 Research Boulevard, Rockville, Maryland, United States, 20850   |
| Public contact               | Eva Kohegyi, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 6095246790, Eva.Kohegyi@otsuka-us.com |
| Scientific contact           | Eva Kohegyi, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 6095246790, Eva.Kohegyi@otsuka-us.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

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**Results analysis stage**

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|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 04 December 2013  |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 03 September 2013 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 03 September 2013 |
| Was the trial ended prematurely?                     | No                |

Notes:

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**General information about the trial**

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Main objective of the trial:

To compare the efficacy of aripiprazole with placebo in the suppression of tics in children and adolescents (7-17 years) with a diagnosis of Tourette's Disorder (TD) and to evaluate the safety and tolerability of aripiprazole once-daily treatment with oral tablets in children and adolescents with a diagnosis of TD.

Protection of trial subjects:

This study was designed and monitored in compliance with the protocol and in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline, and the applicable local laws and regulatory requirements of the countries in which the trial was conducted.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 November 2012 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Canada: 27        |
| Country: Number of subjects enrolled | Hungary: 9        |
| Country: Number of subjects enrolled | Italy: 5          |
| Country: Number of subjects enrolled | United States: 92 |
| Worldwide total number of subjects   | 133               |
| EEA total number of subjects         | 14                |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 66 |
| Adolescents (12-17 years)                 | 67 |

|                      |   |
|----------------------|---|
| Adults (18-64 years) | 0 |
| From 65 to 84 years  | 0 |
| 85 years and over    | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial in children and adolescents (aged 7-17 years) with TD. 171 participants were screened, of which 133 were randomized to treatment.

### Pre-assignment

Screening details:

The trial consisted of a pretreatment phase and a treatment phase. Pretreatment phase consisted of a screening and washout (when applicable) period. This was followed by an 8-week treatment phase starting with the baseline visit (Day 0). Participants were randomized 1:1:1 to aripiprazole high dose, aripiprazole low dose or placebo.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator          |

Blinding implementation details:

During the trial, the treatment assignment code list was available only to an independent biostatistician. Except in cases of emergency unblinding, subjects, investigational site personnel, OPDC 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 had been locked.

### Arms

|                              |                       |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes                   |
| <b>Arm title</b>             | Aripiprazole low dose |

Arm description:

For participants who weighed < 50 kg at baseline, low dose was 5 mg/day. For participants who weighed ≥ 50 kg at baseline, low dose was 10 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was titrated to achieve the randomized dose. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Aripiprazole       |
| Investigational medicinal product code |                    |
| Other name                             | Abilify, OPC-14597 |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |

Dosage and administration details:

For participants who weighed < 50 kg at baseline, low dose was one 5 mg/day plus 1 placebo tablet. For participants who weighed ≥ 50 kg at baseline, low dose was one 10 mg/day and 1 placebo tablet.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Aripiprazole high dose |
|------------------|------------------------|

Arm description:

For participants who weighed < 50 kg at baseline, high dose was 10 mg/day. For participants who weighed ≥ 50 kg at baseline, high dose was 20 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was then titrated weekly until the randomized dose was achieved. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Aripiprazole       |
| Investigational medicinal product code |                    |
| Other name                             | Abilify, OPC-14597 |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |

Dosage and administration details:

For participants who weighed < 50 kg at baseline, high dose was 10 mg/day plus 1 placebo tablet. For participants who weighed ≥ 50 kg at baseline, high dose was two 10 mg/day plus no placebo tablet.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Participants received matching placebo tablets in the same way as aripiprazole.

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Matching placebo tablets in the same way as aripiprazole.

| <b>Number of subjects in period 1</b> | Aripiprazole low dose | Aripiprazole high dose | Placebo |
|---------------------------------------|-----------------------|------------------------|---------|
| Started                               | 44                    | 45                     | 44      |
| Completed                             | 42                    | 35                     | 42      |
| Not completed                         | 2                     | 10                     | 2       |
| Consent withdrawn by subject          | -                     | 3                      | 1       |
| Adverse Event                         | -                     | 7                      | 1       |
| Protocol Violation                    | 2                     | -                      | -       |

## Baseline characteristics

### Reporting groups

|   |                        |
|---|------------------------|
| Reporting group title   | Aripiprazole low dose  |
| Reporting group description:  |                        |
| For participants who weighed < 50 kg at baseline, low dose was 5 mg/day. For participants who weighed ≥ 50 kg at baseline, low dose was 10 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was titrated to achieve the randomized dose. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.                        |                        |
| Reporting group title   | Aripiprazole high dose |
| Reporting group description:  |                        |
| For participants who weighed < 50 kg at baseline, high dose was 10 mg/day. For participants who weighed ≥ 50 kg at baseline, high dose was 20 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was then titrated weekly until the randomized dose was achieved. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose. |                        |
| Reporting group title   | Placebo                |
| Reporting group description:  |                        |
| Participants received matching placebo tablets in the same way as aripiprazole.   |                        |

| Reporting group values  | Aripiprazole low dose | Aripiprazole high dose | Placebo |
|---|-----------------------|------------------------|---------|
| Number of subjects  | 44                    | 45                     | 44      |
| Age categorical<br>Units: Subjects  |                       |                        |         |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                       |                        |         |
| Age continuous<br>Units: years  |                       |                        |         |
| arithmetic mean   | 11.1                  | 11.8                   | 11.6    |
| standard deviation  | ± 3.1                 | ± 2.8                  | ± 2.8   |
| Gender categorical<br>Units: Subjects   |                       |                        |         |
| Female  | 8                     | 10                     | 11      |
| Male  | 36                    | 35                     | 33      |

| Reporting group values                             | Total |  |  |
|--|-------|--|--|
| Number of subjects                                 | 133   |  |  |
| Age categorical<br>Units: Subjects                 |       |  |  |
| In utero   | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 0     |  |  |

|  |     |  |  |
|--|-----|--|--|
| Newborns (0-27 days)                     | 0   |  |  |
| Infants and toddlers (28 days-23 months) | 0   |  |  |
| Children (2-11 years)                    | 0   |  |  |
| Adolescents (12-17 years)                | 0   |  |  |
| Adults (18-64 years)                     | 0   |  |  |
| From 65-84 years                         | 0   |  |  |
| 85 years and over                        | 0   |  |  |
| Age continuous                           |     |  |  |
| Units: years                             |     |  |  |
| arithmetic mean                          |     |  |  |
| standard deviation                       | -   |  |  |
| Gender categorical                       |     |  |  |
| Units: Subjects                          |     |  |  |
| Female                                   | 29  |  |  |
| Male                                     | 104 |  |  |

## End points

### End points reporting groups

|   |                        |
|---|------------------------|
| Reporting group title   | Aripiprazole low dose  |
| Reporting group description:<br>For participants who weighed < 50 kg at baseline, low dose was 5 mg/day. For participants who weighed ≥ 50 kg at baseline, low dose was 10 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was titrated to achieve the randomized dose. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.                        |                        |
| Reporting group title   | Aripiprazole high dose |
| Reporting group description:<br>For participants who weighed < 50 kg at baseline, high dose was 10 mg/day. For participants who weighed ≥ 50 kg at baseline, high dose was 20 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was then titrated weekly until the randomized dose was achieved. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose. |                        |
| Reporting group title   | Placebo                |
| Reporting group description:<br>Participants received matching placebo tablets in the same way as aripiprazole.   |                        |

### Primary: Change from Baseline to Week 8 in Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS)

|   |  |
|---|--|
| End point title   | Change from Baseline to Week 8 in Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS) |
| End point description:<br>The YGTSS is a semi-structured clinical interview designed to measure current (time frame of the past 1 week) tic severity. This scale consists of a tic inventory, with 5 separate rating scales to rate the severity of symptoms, and an impairment ranking. Ratings are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics each, including number, frequency, intensity, complexity, and interference. Summation of these 10 scores (ie, 0-50) provides a TTS that was the primary outcome measure in this trial. The YGTSS ranking of impairment score rated on a 50-point scale anchored from 0 (no impairment) to 50 (severe impairment) to assess impairment experienced in areas of self-esteem, family life, social acceptance, and school scores. Intent-to-Treat (ITT) Population: All participants randomly assigned to the double-blind treatment. Ns are number of participants with Baseline and a Week-8 assessment of the given variable. |  |
| End point type  | Primary  |
| End point timeframe:<br>Baseline to Week 8  |  |

| End point values                    | Aripiprazole low dose | Aripiprazole high dose | Placebo         |  |
|-------------------------------------|-----------------------|------------------------|-----------------|--|
| Subject group type                  | Reporting group       | Reporting group        | Reporting group |  |
| Number of subjects analysed         | 42                    | 35                     | 42              |  |
| Units: Units on a scale             |                       |                        |                 |  |
| least squares mean (standard error) | -13.35 (± 1.59)       | -16.94 (± 1.61)        | -7.09 (± 1.55)  |  |



## Statistical analyses

| Statistical analysis title   | Statistical analysis 1 at Week 8 |
|--|----------------------------------|
| Statistical analysis description:  |                                  |
| Assuming 5% of participants may drop out of the trial without a post-baseline efficacy evaluation, a total of 126 participants were required to provide at least 80% power to detect a treatment difference of -5 (common standard deviation [SD] of 8.5) between at least 1 of 2 aripiprazole dose levels and placebo in the primary outcome. |                                  |
| Comparison groups  | Aripiprazole low dose v Placebo  |
| Number of subjects included in analysis  | 84                               |
| Analysis specification   | Pre-specified                    |
| Analysis type  | superiority                      |
| P-value  | = 0.002 <sup>[1]</sup>           |
| Method   | Mixed models analysis            |
| Parameter estimate   | Treatment difference             |
| Point estimate   | -6.26                            |
| Confidence interval  |                                  |
| level  | 95 %                             |
| sides  | 2-sided                          |
| lower limit  | -10.18                           |
| upper limit  | -2.34                            |

Notes:

[1] - The Hochberg procedure was used to adjust for multiplicity.

| Statistical analysis title   | Statistical analysis 2 at Week 8 |
|--|----------------------------------|
| Statistical analysis description:  |                                  |
| Assuming 5% of participants may drop out of the trial without a post-baseline efficacy evaluation, a total of 126 participants were required to provide at least 80% power to detect a treatment difference of -5 (common standard SD of 8.5) between at least 1 of 2 aripiprazole dose levels and placebo in the primary outcome. |                                  |
| Comparison groups  | Placebo v Aripiprazole high dose |
| Number of subjects included in analysis  | 77                               |
| Analysis specification   | Pre-specified                    |
| Analysis type  | superiority                      |
| P-value  | < 0.0001 <sup>[2]</sup>          |
| Method   | Mixed models analysis            |
| Parameter estimate   | Treatment difference             |
| Point estimate   | -9.85                            |
| Confidence interval  |                                  |
| level  | 95 %                             |
| sides  | 2-sided                          |
| lower limit  | -13.84                           |
| upper limit  | -5.86                            |

Notes:

[2] - The Hochberg procedure was used to adjust for multiplicity.

## Secondary: Change in Clinical Global Impressions Scale-Tourette's Syndrome (CGI-TS) Score at Week 8

|                 |  |
|-----------------|--|
| End point title | Change in Clinical Global Impressions Scale-Tourette's Syndrome (CGI-TS) Score at Week 8 |
|-----------------|--|

End point description:

To assess CGI-TS severity, the rater or physician answered the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" The

change score was obtained from CGI-TS improvement scale assessment: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. ITT Population: All participants randomly assigned to the double-blind treatment. At Week 8, data were available for 42 participants in the low dose, 35 in the high dose and 42 in the placebo group.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 8               |           |

| End point values                    | Aripiprazole low dose | Aripiprazole high dose | Placebo           |  |
|-------------------------------------|-----------------------|------------------------|-------------------|--|
| Subject group type                  | Reporting group       | Reporting group        | Reporting group   |  |
| Number of subjects analysed         | 42                    | 35                     | 42                |  |
| Units: Units on a scale             |                       |                        |                   |  |
| least squares mean (standard error) | 2.12 ( $\pm$ 0.21)    | 2.13 ( $\pm$ 0.21)     | 3.15 ( $\pm$ 0.2) |  |

## Statistical analyses

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 1 at Week 8 |
| Comparison groups                       | Aripiprazole low dose v Placebo  |
| Number of subjects included in analysis | 84                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.0002 <sup>[3]</sup>          |
| Method                                  | Mixed models analysis            |
| Parameter estimate                      | Treatment difference             |
| Point estimate                          | -1.03                            |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -1.54                            |
| upper limit                             | -0.52                            |

Notes:

[3] - The Hochberg procedure was used to adjust for multiplicity.

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 2 at Week 8 |
| Comparison groups                       | Aripiprazole high dose v Placebo |
| Number of subjects included in analysis | 77                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.0002 <sup>[4]</sup>          |
| Method                                  | Mixed models analysis            |
| Parameter estimate                      | Treatment difference             |
| Point estimate                          | -1.02                            |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -1.54   |
| upper limit         | -0.49   |

Notes:

[4] - The Hochberg procedure was used to adjust for multiplicity.

## Secondary: Mean change from Baseline to Endpoint (Week 8) in Total YGTSS Score

|                 |   |
|-----------------|---|
| End point title | Mean change from Baseline to Endpoint (Week 8) in Total YGTSS Score |
|-----------------|---|

End point description:

The YGTSS consists of a tic inventory, with 5 separate rating scales to rate the severity of symptoms (on a scale of 0 to 5 for 5 different dimensions, including number, frequency, intensity, complexity, and interference) of motor and vocal tics, and an impairment ranking. The Total YGTSS score is the summation of the severity scores of motor and vocal tics and also the ranking of impairment (range of 0 to 100). A missing value of a YGTSS item scale could result in a missing Total YGTSS score. A reduction in Total YGTSS score from baseline represents an improvement in symptoms. ITT Population: All participants randomly assigned to the double-blind treatment. At Week 8, data were available for 42 participants in the low dose, 35 in the high dose and 42 in the placebo group.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 8

| End point values                    | Aripiprazole low dose | Aripiprazole high dose | Placebo         |  |
|-------------------------------------|-----------------------|------------------------|-----------------|--|
| Subject group type                  | Reporting group       | Reporting group        | Reporting group |  |
| Number of subjects analysed         | 42                    | 35                     | 42              |  |
| Units: Units on a scale             |                       |                        |                 |  |
| least squares mean (standard error) | -26.69 (± 3.34)       | -32.8 (± 3.39)         | -13.43 (± 3.27) |  |

## Statistical analyses

|   |                                  |
|---|----------------------------------|
| Statistical analysis title              | Statistical analysis 1 at Week 8 |
| Comparison groups                       | Aripiprazole low dose v Placebo  |
| Number of subjects included in analysis | 84                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.0017 <sup>[5]</sup>          |
| Method                                  | Mixed models analysis            |
| Parameter estimate                      | Treatment difference             |
| Point estimate                          | -13.26                           |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -21.43                           |
| upper limit                             | -5.08                            |

Notes:

[5] - Treatment, week, treatment by week interaction, region, and weight group were fixed categorical effects; baseline value as a fixed covariate.

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 2 at Week 8 |
| Comparison groups                       | Aripiprazole high dose v Placebo |
| Number of subjects included in analysis | 77                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | < 0.0001 <sup>[6]</sup>          |
| Method                                  | Mixed models analysis            |
| Parameter estimate                      | Treatment difference             |
| Point estimate                          | -19.37                           |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -27.7                            |
| upper limit                             | -11.04                           |

Notes:

[6] - Treatment, week, treatment by week interaction, region, and weight group were fixed categorical effects; baseline value as a fixed covariate.

### Secondary: Mean change from Baseline to Endpoint (Week 8) in CGI-TS Severity Score

|                 |   |
|-----------------|---|
| End point title | Mean change from Baseline to Endpoint (Week 8) in CGI-TS Severity Score |
|-----------------|---|

End point description:

The CGI-TS Severity scale (range 0-7) is a single-item rating score, with higher scores representing greater severity or less improvement. A response of 0 (not assessed) is considered and handled as missing data. ITT Population: All participants randomly assigned to the double-blind treatment. At Week 8, data were available for 42 participants in the low dose, 35 in the high dose and 42 in the placebo group.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 8

|                                     |                       |                        |                 |  |
|-------------------------------------|-----------------------|------------------------|-----------------|--|
| <b>End point values</b>             | Aripiprazole low dose | Aripiprazole high dose | Placebo         |  |
| Subject group type                  | Reporting group       | Reporting group        | Reporting group |  |
| Number of subjects analysed         | 42                    | 35                     | 42              |  |
| Units: Units on a scale             |                       |                        |                 |  |
| least squares mean (standard error) | -1.35 (± 0.19)        | -1.47 (± 0.19)         | -0.55 (± 0.19)  |  |

### Statistical analyses

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 1 at Week 8 |
| Comparison groups                 | Aripiprazole low dose v Placebo  |

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 84                     |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.001 <sup>[7]</sup> |
| Method                                  | Mixed models analysis  |
| Parameter estimate                      | Treatment difference   |
| Point estimate                          | -0.8                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | -1.27                  |
| upper limit                             | -0.33                  |

Notes:

[7] - Treatment, week, treatment by week interaction, region, and weight group were fixed categorical effects; baseline value as a fixed covariate.

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 2 at Week 8 |
| Comparison groups                       | Aripiprazole high dose v Placebo |
| Number of subjects included in analysis | 77                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.0002 <sup>[8]</sup>          |
| Method                                  | Mixed models analysis            |
| Parameter estimate                      | Treatment difference             |
| Point estimate                          | -0.92                            |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -1.41                            |
| upper limit                             | -0.44                            |

Notes:

[8] - Treatment, week, treatment by week interaction, region, and weight group were fixed categorical effects; baseline value as a fixed covariate.

## Secondary: Response Rate

|  |               |
|--|---------------|
| End point title  | Response Rate |
| End point description:   |               |
| Clinical response is defined as > 25% improvement from baseline to Week 8 in YGTSS TTS or a CGI-TS Change score of 1 [very much improved] or 2 [much improved] at Week 8. Response will be considered as missing only if both YGTSS TTS and CGI-TS change score are missing. As long as one of them is non-missing, response outcome will be determined based on the non-missing score. ITT Population: All participants randomly assigned to the double-blind treatment. At Week 8, data were available for 42 participants in the low dose, 35 in the high dose and 42 in the placebo group. |               |
| End point type   | Secondary     |
| End point timeframe:   |               |
| Week 8   |               |

| End point values                  | Aripiprazole low dose | Aripiprazole high dose | Placebo         |  |
|-----------------------------------|-----------------------|------------------------|-----------------|--|
| Subject group type                | Reporting group       | Reporting group        | Reporting group |  |
| Number of subjects analysed       | 42                    | 35                     | 42              |  |
| Units: Percentage of participants |                       |                        |                 |  |
| number (not applicable)           | 73.8                  | 88.6                   | 54.8            |  |

## Statistical analyses

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 1 at Week 8 |
| Comparison groups                       | Aripiprazole low dose v Placebo  |
| Number of subjects included in analysis | 84                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.0835 <sup>[9]</sup>          |
| Method                                  | Cochran-Mantel-Haenszel          |
| Parameter estimate                      | Response ratio                   |
| Point estimate                          | 1.36                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.98                             |
| upper limit                             | 1.88                             |

Notes:

[9] - P-value derived from Cochran-Mantel-Haenszel (CMH) General Association Test adjusting for region and weight group. The response ratio >1 favours aripiprazole.

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 2 at Week 8 |
| Comparison groups                       | Aripiprazole high dose v Placebo |
| Number of subjects included in analysis | 77                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.0014 <sup>[10]</sup>         |
| Method                                  | Cochran-Mantel-Haenszel          |
| Parameter estimate                      | Response ratio                   |
| Point estimate                          | 1.61                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 1.2                              |
| upper limit                             | 2.16                             |

Notes:

[10] - P-value derived from CMH General Association Test adjusting for region and weight group. The response ratio >1 favours aripiprazole.

## Secondary: Treatment discontinuation rate

|                 |                                |
|-----------------|--------------------------------|
| End point title | Treatment discontinuation rate |
|-----------------|--------------------------------|

End point description:

Treatment discontinuation rate will be calculated as the number of discontinued participants (ie, those who were withdrawn from the trial without completing the Week 8 visit) over the number of all randomized participants. ITT Population: All participants randomly assigned to the double-blind

treatment.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 8               |           |

| End point values                  | Aripiprazole low dose | Aripiprazole high dose | Placebo         |  |
|-----------------------------------|-----------------------|------------------------|-----------------|--|
| Subject group type                | Reporting group       | Reporting group        | Reporting group |  |
| Number of subjects analysed       | 44                    | 45                     | 44              |  |
| Units: Percentage of participants |                       |                        |                 |  |
| number (not applicable)           | 4.5                   | 22.5                   | 4.5             |  |

### Statistical analyses

| Statistical analysis title              | Statistical analysis 1 at Week 8 |
|---|----------------------------------|
| Comparison groups                       | Placebo v Aripiprazole low dose  |
| Number of subjects included in analysis | 88                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.9187 <sup>[11]</sup>         |
| Method                                  | Cochran-Mantel-Haenszel          |
| Parameter estimate                      | Discontinuation ratio            |
| Point estimate                          | 1.16                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.19                             |
| upper limit                             | 7.05                             |

Notes:

[11] - Discontinuation ratio < 1 favors aripiprazole. P-value derived from CMH General Association Test adjusting for region and weight group.

| Statistical analysis title              | Statistical analysis 2 at Week 8 |
|---|----------------------------------|
| Comparison groups                       | Placebo v Aripiprazole low dose  |
| Number of subjects included in analysis | 88                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.9576 <sup>[12]</sup>         |
| Method                                  | Regression, Cox                  |
| Parameter estimate                      | Hazard ratio (HR)                |
| Point estimate                          | 1.05                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.19                             |
| upper limit                             | 7.05                             |

Notes:

[12] - Hazard ratio < 1 favors aripiprazole. P-value derived from Cox proportional hazard regression adjusting for region and weight group.

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 3 at Week 8 |
| Comparison groups                       | Aripiprazole high dose v Placebo |
| Number of subjects included in analysis | 89                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.0132 <sup>[13]</sup>         |
| Method                                  | Cochran-Mantel-Haenszel          |
| Parameter estimate                      | Discontinuation ratio            |
| Point estimate                          | 4.06                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 1.1                              |
| upper limit                             | 14.95                            |

Notes:

[13] - Discontinuation ratio < 1 favors aripiprazole. P-value derived from CMH General Association Test adjusting for region and weight group.

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 4 at Week 8 |
| Comparison groups                       | Placebo v Aripiprazole high dose |
| Number of subjects included in analysis | 89                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.0278 <sup>[14]</sup>         |
| Method                                  | Regression, Cox                  |
| Parameter estimate                      | Hazard ratio (HR)                |
| Point estimate                          | 5.51                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 1.1                              |
| upper limit                             | 14.95                            |

Notes:

[14] - Hazard ratio < 1 favors aripiprazole. P-value derived from Cox proportional hazard regression adjusting for region and weight group.



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from the time of signing the informed consent up to 30 days after the last trial visit.

Adverse event reporting additional description:

An AE is defined as any untoward medical occurrence with the use of study drug. AE was considered serious if fatal, life threatening, disabling or incapacitating, required in participant hospitalization or prolonged hospitalization, congenital anomaly/birth defect or other medically significant event.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Aripiprazole low dose |
|-----------------------|-----------------------|

Reporting group description:

For participants who weighed < 50 kg at baseline, low dose was 5 mg/day. For participants who weighed ≥ 50 kg at baseline, low dose was 10 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was titrated to achieve the randomized dose. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Aripiprazole high dose |
|-----------------------|------------------------|

Reporting group description:

For participants who weighed < 50 kg at baseline, high dose was 10 mg/day. For participants who weighed ≥ 50 kg at baseline, high dose was 20 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was then titrated weekly until the randomized dose was achieved. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received matching placebo tablets in the same way as aripiprazole.

| Serious adverse events                            | Aripiprazole low dose | Aripiprazole high dose | Placebo        |
|---|-----------------------|------------------------|----------------|
| Total subjects affected by serious adverse events |                       |                        |                |
| subjects affected / exposed                       | 0 / 44 (0.00%)        | 0 / 45 (0.00%)         | 0 / 44 (0.00%) |
| number of deaths (all causes)                     | 0                     | 0                      | 0              |
| number of deaths resulting from adverse events    | 0                     | 0                      | 0              |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events                            | Aripiprazole low dose | Aripiprazole high dose | Placebo         |
|---|-----------------------|------------------------|-----------------|
| Total subjects affected by non-serious adverse events |                       |                        |                 |
| subjects affected / exposed                           | 21 / 44 (47.73%)      | 29 / 45 (64.44%)       | 8 / 44 (18.18%) |

|  |                 |                 |                |
|--|-----------------|-----------------|----------------|
| Nervous system disorders                             |                 |                 |                |
| Akathisia  |                 |                 |                |
| subjects affected / exposed                          | 0 / 44 (0.00%)  | 3 / 45 (6.67%)  | 0 / 44 (0.00%) |
| occurrences (all)                                    | 0               | 3               | 0              |
| Headache   |                 |                 |                |
| subjects affected / exposed                          | 3 / 44 (6.82%)  | 4 / 45 (8.89%)  | 1 / 44 (2.27%) |
| occurrences (all)                                    | 3               | 4               | 1              |
| Lethargy   |                 |                 |                |
| subjects affected / exposed                          | 0 / 44 (0.00%)  | 5 / 45 (11.11%) | 0 / 44 (0.00%) |
| occurrences (all)                                    | 0               | 5               | 0              |
| Sedation   |                 |                 |                |
| subjects affected / exposed                          | 8 / 44 (18.18%) | 4 / 45 (8.89%)  | 1 / 44 (2.27%) |
| occurrences (all)                                    | 8               | 5               | 1              |
| Somnolence   |                 |                 |                |
| subjects affected / exposed                          | 5 / 44 (11.36%) | 7 / 45 (15.56%) | 1 / 44 (2.27%) |
| occurrences (all)                                    | 5               | 7               | 1              |
| General disorders and administration site conditions |                 |                 |                |
| Fatigue  |                 |                 |                |
| subjects affected / exposed                          | 3 / 44 (6.82%)  | 7 / 45 (15.56%) | 0 / 44 (0.00%) |
| occurrences (all)                                    | 3               | 7               | 0              |
| Gastrointestinal disorders                           |                 |                 |                |
| Nausea   |                 |                 |                |
| subjects affected / exposed                          | 3 / 44 (6.82%)  | 4 / 45 (8.89%)  | 1 / 44 (2.27%) |
| occurrences (all)                                    | 3               | 4               | 1              |
| Vomiting   |                 |                 |                |
| subjects affected / exposed                          | 2 / 44 (4.55%)  | 3 / 45 (6.67%)  | 2 / 44 (4.55%) |
| occurrences (all)                                    | 2               | 4               | 2              |
| Psychiatric disorders                                |                 |                 |                |
| Restlessness   |                 |                 |                |
| subjects affected / exposed                          | 0 / 44 (0.00%)  | 3 / 45 (6.67%)  | 1 / 44 (2.27%) |
| occurrences (all)                                    | 0               | 3               | 1              |
| Infections and infestations                          |                 |                 |                |
| Nasopharyngitis                                      |                 |                 |                |
| subjects affected / exposed                          | 3 / 44 (6.82%)  | 4 / 45 (8.89%)  | 0 / 44 (0.00%) |
| occurrences (all)                                    | 3               | 4               | 0              |
| Upper respiratory tract infection                    |                 |                 |                |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)   | 1 / 44 (2.27%)<br>1 | 1 / 45 (2.22%)<br>1 | 3 / 44 (6.82%)<br>4 |
| Metabolism and nutrition disorders<br>Increased appetite<br>subjects affected / exposed<br>occurrences (all) | 4 / 44 (9.09%)<br>4 | 3 / 45 (6.67%)<br>3 | 1 / 44 (2.27%)<br>1 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 16 October 2012 | Protocol amendment 1 clarified the concomitant use of benzodiazepines, changed the titration scheme, specified the entire Swanson, Nolan and Pelham-IV (SNAP-IV) rating scale, rather than the attention-deficit/hyperactivity disorder (ADHD) subscales; removed the Gilles de la Tourette Syndrome-Quality of Life scale assessments; added weight-based dosing stratification. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported