



Clinical trial results:

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

| | |
|--------------------------|----------------|
| EudraCT number | 2011-000468-83 |
| Trial protocol | DE BG |
| Global end of trial date | 12 March 2014 |

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 | 31-10-273 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| 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, MD, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 609 524 6790, Eva.Kohegyi@otsuka-us.com |
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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:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 August 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 March 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 March 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Primary objective was 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. The primary efficacy measure is change from Baseline to endpoint (Week 8) on the Total Tic score (TTS) of the Yale Global Tic Severity Scale (YGTSS). Secondary efficacy measures included Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) and Gilles de la Tourette Syndrome - Quality of Life Scale (GTS-QOL). The secondary objective was to evaluate the safety and tolerability of aripiprazole once-weekly treatment with oral tablets in children and adolescents with Tourette's Disorder.

Protection of trial subjects:

This trial was conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable local laws and regulatory requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 02 August 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Romania: 15 |
| Country: Number of subjects enrolled | Ukraine: 27 |
| Country: Number of subjects enrolled | United States: 30 |
| Country: Number of subjects enrolled | Bulgaria: 5 |
| Country: Number of subjects enrolled | Germany: 6 |
| Worldwide total number of subjects | 83 |
| EEA total number of subjects | 26 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| 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) | 39 |
| Adolescents (12-17 years) | 44 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in 83 participants at 38 trial sites in the following 5 countries: Bulgaria, Germany, Romania, Ukraine, and the United States.

Pre-assignment

Screening details:

This trial consisted of 2 distinct phases: a pre-treatment phase and a treatment phase. The pre-treatment phase consisted of a screening period, a washout period, and a Baseline visit. This was followed by an 8-week treatment phase. There was a follow-up period (30 ± 3 days) for those participants who did not roll-over into the open-label trial.

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:

The blind was not broken for any participants before database lock.

Arms

| | |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Aripiprazole 52.5 mg |

Arm description:

Participants were administered aripiprazole orally with a dose of 52.5 milligram (mg) weekly for the 8-week treatment phase.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Aripiprazole enteric-coated extended-release (ECER) Tablets 52.5 mg |
| Investigational medicinal product code | |
| Other name | Aripiprazole, OPC-14597 |
| Pharmaceutical forms | Prolonged-release tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants were administered a dosage of 52.5 mg aripiprazole tablets orally weekly

| | |
|------------------|----------------------|
| Arm title | Aripiprazole 77.5 mg |
|------------------|----------------------|

Arm description:

Participants were administered 77.5 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Aripiprazole ECER Tablets 77.5 mg |
| Investigational medicinal product code | |
| Other name | Aripiprazole, OPC-14597 |
| Pharmaceutical forms | Prolonged-release tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants were administered a dosage of 77.5 mg aripiprazole tablets orally weekly

| | |
|------------------|---------------------|
| Arm title | Aripiprazole 110 mg |
|------------------|---------------------|

Arm description:

Participants were administered 110 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Aripiprazole ECER Tablets 110 mg |
| Investigational medicinal product code | |
| Other name | Aripiprazole, OPC-14597 |
| Pharmaceutical forms | Prolonged-release tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants were administered a dosage of 110 mg aripiprazole tablets orally weekly

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Participants were administered matching placebo tablets weekly

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

Dosage and administration details:

Participants were administered matching placebo tablets in the same way as aripiprazole

| Number of subjects in period 1 | Aripiprazole 52.5 mg | Aripiprazole 77.5 mg | Aripiprazole 110 mg |
|---------------------------------------|----------------------|----------------------|---------------------|
| Started | 20 | 21 | 21 |
| Completed | 17 | 17 | 16 |
| Not completed | 3 | 4 | 5 |
| Consent withdrawn by subject | - | 1 | 2 |
| Adverse Event | - | 1 | - |
| Lost to follow-up | 2 | - | - |
| Sponsor Discontinued Trial | - | 2 | 2 |
| Lack of efficacy | 1 | - | - |
| Protocol deviation | - | - | 1 |

| Number of subjects in period 1 | Placebo |
|---------------------------------------|---------|
| Started | 21 |
| Completed | 18 |
| Not completed | 3 |
| Consent withdrawn by subject | 1 |
| Adverse Event | - |
| Lost to follow-up | - |
| Sponsor Discontinued Trial | 2 |
| Lack of efficacy | - |
| Protocol deviation | - |

Baseline characteristics

Reporting groups

| | |
|--|----------------------|
| Reporting group title | Aripiprazole 52.5 mg |
| Reporting group description: Participants were administered aripiprazole orally with a dose of 52.5 milligram (mg) weekly for the 8-week treatment phase. | |
| Reporting group title | Aripiprazole 77.5 mg |
| Reporting group description: Participants were administered 77.5 mg of aripiprazole oral tablets weekly for the 8-week treatment phase. | |
| Reporting group title | Aripiprazole 110 mg |
| Reporting group description: Participants were administered 110 mg of aripiprazole oral tablets weekly for the 8-week treatment phase. | |
| Reporting group title | Placebo |
| Reporting group description: Participants were administered matching placebo tablets weekly | |

| Reporting group values | Aripiprazole 52.5 mg | Aripiprazole 77.5 mg | Aripiprazole 110 mg |
|---|----------------------|----------------------|---------------------|
| Number of subjects | 20 | 21 | 21 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 11.5 | 11.7 | 12.5 |
| standard deviation | ± 3.4 | ± 2.8 | ± 2.7 |
| Gender categorical Units: Subjects | | | |
| Female | 3 | 8 | 3 |
| Male | 17 | 13 | 18 |

| Reporting group values | Placebo | Total | |
|--|---------|-------|--|
| Number of subjects | 21 | 83 | |
| Age categorical 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 | 11.8 | | |
| standard deviation | ± 2.7 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 6 | 20 | |
| Male | 15 | 63 | |

End points

End points reporting groups

| | |
|--|----------------------|
| Reporting group title | Aripiprazole 52.5 mg |
| Reporting group description: Participants were administered aripiprazole orally with a dose of 52.5 milligram (mg) weekly for the 8-week treatment phase. | |
| Reporting group title | Aripiprazole 77.5 mg |
| Reporting group description: Participants were administered 77.5 mg of aripiprazole oral tablets weekly for the 8-week treatment phase. | |
| Reporting group title | Aripiprazole 110 mg |
| Reporting group description: Participants were administered 110 mg of aripiprazole oral tablets weekly for the 8-week treatment phase. | |
| Reporting group title | Placebo |
| Reporting group description: Participants were administered matching placebo tablets weekly | |

Primary: Mean change from Baseline to Week 8 in Yale Global Tic Severity Scale (YGTSS) total tic score

| | |
|---|--|
| End point title | Mean change from Baseline to Week 8 in Yale Global Tic Severity Scale (YGTSS) total tic score ^[1] |
| End point description: The YGTSS is a semi-structured clinical interview designed to measure current tic severity. This scale consisted of a tic inventory, with 5 separate rating scales to rate the severity of symptoms, and an impairment ranking. Ratings were 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. The total tic score (TTS) ranged from 0 (none) to 50 (severe) with higher score for more severe symptoms (greater reduction from baseline for greater improvement). The YGTSS ranking of impairment, with a maximum of 50 points, is based on the impact of the tic disorder on areas of self esteem, family life, social acceptance and school scores. This is a fully validated scale in adults and has become a standard instrument for the evaluation of the severity of Tourette's Disorder in children. In an Intent-to-Treat (ITT) population, participants were randomly assigned to the double-blind treatment. | |
| End point type | Primary |
| End point timeframe: Baseline to Week 8 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were defined for this endpoint because the trial was discontinued by the sponsor with a much smaller sample size than originally planned.

| End point values | Aripiprazole 52.5 mg | Aripiprazole 77.5 mg | Aripiprazole 110 mg | Placebo |
|--------------------------------------|----------------------|----------------------|---------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 17 | 17 | 16 | 18 |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -8.2 (± 4.8) | -9.9 (± 6.7) | -14.5 (± 7.7) | -9.6 (± 7.5) |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) change score at Week 8

| | |
|------------------------|--|
| End point title | Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) change score at Week 8 |
| End point description: | The severity of illness and efficacy of study medication for each participant were rated using the CGI-TS scale. The study physician were to rate the participants total improvement whether or not it is due to study treatment. All responses were compared to the participants condition at Baseline (Day 0). Response choices include: 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. |
| End point type | Secondary |
| End point timeframe: | |
| Week 8 | |

| End point values | Aripiprazole 52.5 mg | Aripiprazole 77.5 mg | Aripiprazole 110 mg | Placebo |
|--------------------------------------|-------------------------|-------------------------|------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 17 | 16 | 16 | 18 |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 2.7 (± 1) | 2.8 (± 0.8) | 2.3 (± 1.1) | 2.6 (± 0.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Gilles de la Tourette Quality of Life (GTS-QOL) at Week 8

| | |
|------------------------|--|
| End point title | Mean change from Baseline in Gilles de la Tourette Quality of Life (GTS-QOL) at Week 8 |
| End point description: | The GTS-QOL is a disease-specific patient-reported scale for the measurement of health-related quality of life in participants with Tourette's Disorder, taking into account the complexity of the clinical picture of the disease. The questionnaire consists of a 27-item Tourette's Disorder-specific scale with 4 subscales (psychological, physical, obsessional, and cognitive). The GTS-QOL total score ranged from 0 (extremely dissatisfied with life) and 100 (extremely satisfied with life). |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 8 | |

| End point values | Aripiprazole 52.5 mg | Aripiprazole 77.5 mg | Aripiprazole 110 mg | Placebo |
|--------------------------------------|-------------------------|-------------------------|------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 17 | 17 | 16 | 18 |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 8.8 (± 14.1) | 3.8 (± 24.4) | 13.1 (± 20.9) | 13.4 (± 15.9) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the signing of the informed consent until the follow-up visit 30 (\pm 3) days.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Aripiprazole 52.5 mg |
|-----------------------|----------------------|

Reporting group description:

Participants were administered aripiprazole orally with a dose of 52.5 mg weekly for the 8-week treatment phase.

| | |
|-----------------------|----------------------|
| Reporting group title | Aripiprazole 77.5 mg |
|-----------------------|----------------------|

Reporting group description:

Participants were administered 77.5 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.

| | |
|-----------------------|---------------------|
| Reporting group title | Aripiprazole 110 mg |
|-----------------------|---------------------|

Reporting group description:

Participants were administered 110 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.

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

Reporting group description:

Participants were administered matching placebo tablets weekly

| Serious adverse events | Aripiprazole 52.5 mg | Aripiprazole 77.5 mg | Aripiprazole 110 mg |
|---|----------------------|----------------------|---------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Placebo | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Aripiprazole 52.5 mg | Aripiprazole 77.5 mg | Aripiprazole 110 mg |
|---|----------------------|----------------------|---------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 20 (40.00%) | 8 / 21 (38.10%) | 17 / 21 (80.95%) |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | 4 / 21 (19.05%) |
| occurrences (all) | 0 | 1 | 5 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 1 | 1 |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|----------------|----------------|----------------|
| Anxiety | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 0 | 1 |
| Apathy | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Hallucination, auditory | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Restlessness | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Investigations | | | |
| Blood prolactin decreased | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 0 | 1 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|--------------------------------------|-----------------|-----------------|-----------------|
| Palpitations | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervous system disorders | | | |
| Akathisia | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 2 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 21 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 2 | 0 | 3 |
| Headache | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 2 / 21 (9.52%) | 8 / 21 (38.10%) |
| occurrences (all) | 2 | 3 | 10 |
| Hypotonia | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sedation | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Slow response to stimuli | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 3 / 21 (14.29%) | 6 / 21 (28.57%) |
| occurrences (all) | 1 | 11 | 9 |
| Tremor | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|----------------------|---------------------|----------------------|
| Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Eye disorders | | | |
| Ocular hyperaemia subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 21 (4.76%) 1 | 1 / 21 (4.76%) 2 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 21 (4.76%) 1 | 0 / 21 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 1 / 21 (4.76%) 1 | 2 / 21 (9.52%) 2 |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 2 / 21 (9.52%) 2 |
| Lip dry subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Nausea subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 0 / 21 (0.00%) 0 | 3 / 21 (14.29%) 3 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 1 / 21 (4.76%) 1 | 2 / 21 (9.52%) 3 |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 21 (4.76%) 1 | 0 / 21 (0.00%) 0 |
| Renal and urinary disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Pollakiuria subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 21 (4.76%) 1 |
| Pain in jaw subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 1 / 21 (4.76%) 3 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 21 (4.76%) 1 | 2 / 21 (9.52%) 2 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 | 2 / 21 (9.52%) 2 |
| Increased appetite subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 21 (4.76%) 1 | 0 / 21 (0.00%) 0 |

| | | | |
|--|-----------------|--|--|
| Non-serious adverse events | Placebo | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 7 / 21 (33.33%) | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|----------------|--|--|
| Fatigue | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hiccups | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Apathy | | | |

| | | | |
|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hallucination, auditory</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Restlessness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 21 (0.00%)</p> <p>0</p> <p>0 / 21 (0.00%)</p> <p>0</p> <p>0 / 21 (0.00%)</p> <p>0</p> <p>0 / 21 (0.00%)</p> <p>0</p> | | |
| <p>Investigations</p> <p>Blood prolactin decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>White blood cell count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 21 (0.00%)</p> <p>0</p> <p>0 / 21 (0.00%)</p> <p>0</p> <p>0 / 21 (0.00%)</p> <p>0</p> | | |
| <p>Injury, poisoning and procedural complications</p> <p>Hand fracture</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Wound</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 21 (4.76%)</p> <p>1</p> <p>0 / 21 (0.00%)</p> <p>0</p> | | |
| <p>Cardiac disorders</p> <p>Atrioventricular block first degree</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Palpitations</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tachycardia</p> | <p>0 / 21 (0.00%)</p> <p>0</p> <p>0 / 21 (0.00%)</p> <p>0</p> | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Nervous system disorders | | | |
| Akathisia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Headache | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | | |
| occurrences (all) | 2 | | |
| Hypotonia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sedation | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |
| Slow response to stimuli | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tremor | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |

| | | | |
|--|---------------------|--|--|
| Ocular hyperaemia subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | | |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Lip dry subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | | |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Renal and urinary disorders | | | |
| Pollakiuria subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|------------------------------------|----------------|--|--|
| disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 14 February 2013 | In protocol amendment 1, substantial revisions were made such as; To remove the option of allowing subjects to roll over into Study 31-10-274 if they terminated early due to lack of efficacy at Week 5 or later in the previous trial; To clarify the criteria for the exclusion of subjects based on QTc values; To increase the expected duration of the entire trial; To update the statistical methods; To clarify the process of breaking the blind; To update the sample handling for blood for metabolic profiling; To update the protocol with new OPDC standard sections on reporting of product quality complaints. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-------------------|--|--------------|
| 03 September 2013 | 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, OPDC discontinued trial 31-10-273 because the aripiprazole 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). | - |

Notes:

Limitations and caveats

None reported