



## Clinical trial results:

### A Randomized, Placebo-controlled Trial to Evaluate the Long-term (ie, Maintenance) Efficacy of Oral Aripiprazole in the Treatment of Pediatric Subjects with Tourette's Disorder

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2018-002270-48 |
| Trial protocol           | HU             |
| Global end of trial date | 30 June 2020   |

#### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 05 March 2021   |
| First version publication date | 08 January 2021   |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Updates in alignment with revised record following QA review from clinicaltrials.gov. |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | 31-14-204 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03661983 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Otsuka Pharmaceutical Development & Commercialization, Inc  |
| Sponsor organisation address | 2440 Research Boulevard, Rockville, United States, 20850  |
| Public contact               | Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 844-687-8522, OtsukaRMReconciliation@rmpdc.org |
| Scientific contact           | Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 844-687-8522, OtsukaRMReconciliation@rmpdc.org |

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? | Yes |

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 30 June 2020 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 30 June 2020 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the trial is to evaluate the long-term efficacy of aripiprazole once-daily treatment with oral tablets in pediatric subjects with TD.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 13 October 2018 |
| 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 | Canada: 9         |
| Country: Number of subjects enrolled | Hungary: 4        |
| Country: Number of subjects enrolled | United States: 23 |
| Worldwide total number of subjects   | 36                |
| EEA total number of subjects         | 4                 |

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)                     | 22 |
| Adolescents (12-17 years)                 | 14 |

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

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 13 investigative sites in Canada, the United States and Hungary from Oct 13, 2018 to Jun 30, 2020.

### Pre-assignment

Screening details:

Pediatric participants with a diagnosis of Tourette's Disorder were enrolled in this to receive oral aripiprazole in an Open-label Stabilization Phase and a Double-blind Randomized Withdrawal Phase and then followed for safety up to 30 days post-last dose.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Open Label Stabilization Phase |
| Is this the baseline period? | Yes                            |
| Allocation method            | Non-randomised - controlled    |
| Blinding used                | Not blinded                    |

### Arms

|           |  |
|-----------|--|
| Arm title | Open Label Stabilization Phase: Aripiprazole |
|-----------|--|

Arm description:

Participants began treatment with aripiprazole at a 2.0 mg/day dose, with the dose titrated to 5.0 mg/day after 2 days. Subsequent dose adjustments were based on the participant's weight to achieve optimum control of tics up to the maximum recommended doses based on the United States Labeling, up to Week 8 and then continued on the most stabilized dose up to minimum Week 14 or maximum Week 20. Participants who met stabilization criteria were randomized to Double-blind Randomization Phase.

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

Dosage and administration details:

Participants received aripiprazole matching-placebo tablets, orally as per the regimen specified in the arm description.

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

Dosage and administration details:

Participants received aripiprazole tablets, orally as per the regimen specified in the arm description.

|                                       |  |
|---------------------------------------|--|
| <b>Number of subjects in period 1</b> | Open Label Stabilization Phase: Aripiprazole |
| Started                               | 36   |
| Completed                             | 25   |
| Not completed                         | 11   |
| Adverse event, non-fatal              | 5  |

|                               |   |
|-------------------------------|---|
| Withdrawal by Parent/Guardian | 2 |
| Study Terminated by Sponsor   | 3 |
| Lack of efficacy              | 1 |

## Period 2

|                              |  |
|------------------------------|--|
| Period 2 title               | Double-blind Randomized Phase          |
| Is this the baseline period? | No                                     |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Carer, Assessor |

## Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | Double Blind Phase: Aripiprazole Full Dose |

### Arm description:

Participants who met stabilization criteria and randomized to receive full dose of aripiprazole i.e. 5 mg or 10 mg for <50 kg participants, and 10 mg or 20 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to 12 weeks in Double-Blind Phase.

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

### Dosage and administration details:

Participants received aripiprazole tablets, orally as per the regimen specified in the arm description.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Double Blind Phase: Aripiprazole Half Dose |
|------------------|--|

### Arm description:

Participants who met stabilization criteria and randomized to receive half dose of aripiprazole i.e. 2 mg or 5 mg for <50 kg participants, and 5 mg or 10 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to 12 weeks in Double-Blind Phase.

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

### Dosage and administration details:

Participants received aripiprazole tablets, orally as per the regimen specified in the arm description.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Double Blind Phase: Placebo |
|------------------|-----------------------------|

### Arm description:

Participants who met randomization criteria and randomized to receive aripiprazole matching-placebo tablets, 2 daily, orally, up to 12 weeks in Double-Blind Phase.

|          |         |
|----------|---------|
| 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:

Participants received aripiprazole matching-placebo tablets, orally as per the regimen specified in the arm description.

| Number of subjects in period 2 | Double Blind Phase:<br>Aripiprazole Full<br>Dose | Double Blind Phase:<br>Aripiprazole Half<br>Dose | Double Blind Phase:<br>Placebo |
|--------------------------------|--|--|--------------------------------|
|                                |  |  |                                |
| Started                        | 9  | 8  | 8                              |
| Completed                      | 7  | 7  | 0                              |
| Not completed                  | 2  | 1  | 8                              |
| Disease Relapse                | -  | -  | 6                              |
| Adverse event, non-fatal       | 1  | -  | -                              |
| Withdrawal by Parent/Guardian  | -  | -  | 1                              |
| Study Terminated by Sponsor    | 1  | 1  | 1                              |

## Baseline characteristics

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Open Label Stabilization Phase: Aripiprazole |
|-----------------------|--|

Reporting group description:

Participants began treatment with aripiprazole at a 2.0 mg/day dose, with the dose titrated to 5.0 mg/day after 2 days. Subsequent dose adjustments were based on the participant's weight to achieve optimum control of tics up to the maximum recommended doses based on the United States Labeling, up to Week 8 and then continued on the most stabilized dose up to minimum Week 14 or maximum Week 20. Participants who met stabilization criteria were randomized to Double-blind Randomization Phase.

| Reporting group values                    | Open Label Stabilization Phase: Aripiprazole | Total |  |
|---|--|-------|--|
| Number of subjects                        | 36   | 36    |  |
| Age categorical                           |  |       |  |
| Units: Subjects                           |  |       |  |
| Children (2-11 years)                     | 22   | 22    |  |
| Adolescents (12-17 years)                 | 14   | 14    |  |
| Age continuous                            |  |       |  |
| Units: years                              |  |       |  |
| arithmetic mean                           | 10.9   |       |  |
| standard deviation                        | ± 3.0  | -     |  |
| Gender categorical                        |  |       |  |
| Units: Subjects                           |  |       |  |
| Female                                    | 6  | 6     |  |
| Male                                      | 30   | 30    |  |
| Ethnicity                                 |  |       |  |
| Units: Subjects                           |  |       |  |
| Hispanic or Latino                        | 7  | 7     |  |
| Not Hispanic or Latino                    | 29   | 29    |  |
| Unknown or Not Reported                   | 0  | 0     |  |
| Race                                      |  |       |  |
| Units: Subjects                           |  |       |  |
| American Indian or Alaska Native          | 1  | 1     |  |
| Asian                                     | 0  | 0     |  |
| Native Hawaiian or Other Pacific Islander | 0  | 0     |  |
| Black or African American                 | 1  | 1     |  |
| White                                     | 32   | 32    |  |
| More than one race                        | 0  | 0     |  |
| Unknown or Not Reported                   | 2  | 2     |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Open Label Stabilization Phase: Aripiprazole |
| Reporting group description:<br>Participants began treatment with aripiprazole at a 2.0 mg/day dose, with the dose titrated to 5.0 mg/day after 2 days. Subsequent dose adjustments were based on the participant's weight to achieve optimum control of tics up to the maximum recommended doses based on the United States Labeling, up to Week 8 and then continued on the most stabilized dose up to minimum Week 14 or maximum Week 20. Participants who met stabilization criteria were randomized to Double-blind Randomization Phase. |  |
| Reporting group title   | Double Blind Phase: Aripiprazole Full Dose   |
| Reporting group description:<br>Participants who met stabilization criteria and randomized to receive full dose of aripiprazole i.e. 5 mg or 10 mg for <50 kg participants, and 10 mg or 20 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to 12 weeks in Double-Blind Phase.   |  |
| Reporting group title   | Double Blind Phase: Aripiprazole Half Dose   |
| Reporting group description:<br>Participants who met stabilization criteria and randomized to receive half dose of aripiprazole i.e. 2 mg or 5 mg for <50 kg participants, and 5 mg or 10 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to 12 weeks in Double-Blind Phase.   |  |
| Reporting group title   | Double Blind Phase: Placebo                  |
| Reporting group description:<br>Participants who met randomization criteria and randomized to receive aripiprazole matching-placebo tablets, 2 daily, orally, up to 12 weeks in Double-Blind Phase.   |  |

### Primary: Percentage of Participants With Relapse During the Double-blind Randomized Withdrawal Phase

|  |  |
|--|--|
| End point title  | Percentage of Participants With Relapse During the Double-blind Randomized Withdrawal Phase <sup>[1]</sup> |
| End point description:<br>Relapse was defined as a loss of $\geq 50\%$ of the improvement experienced during the open-label stabilization phase (i.e., improvement at the last assessment of Yale Global Tic Severity Scale [YGTSS] before randomization) on the Yale Global Tic Severity Scale Total Tic Score (YGTSS TTS). YGTSS provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic symptoms.<br>Intent to Treat (ITT) Sample included all participants who were randomized and received at least 1 dose of randomized Investigational medicinal product (IMP) were included in this dataset and were analyzed according to the treatment group they were randomized to. |  |
| End point type   | Primary  |
| End point timeframe:<br>From Randomization up to 12 weeks in Double-blind Randomized Withdrawal Phase  |  |

#### 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 have been identified for this primary end point.

| End point values                  | Double Blind Phase: Aripiprazole Full Dose | Double Blind Phase: Aripiprazole Half Dose | Double Blind Phase: Placebo |  |
|-----------------------------------|--|--|-----------------------------|--|
| Subject group type                | Reporting group                            | Reporting group                            | Reporting group             |  |
| Number of subjects analysed       | 9  | 8  | 8                           |  |
| Units: percentage of participants |  |  |                             |  |
| number (not applicable)           | 0  | 0  | 75.0                        |  |



## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose up to 30 days after last dose of study drug (Up to approximately 36 weeks)

Adverse event reporting additional description:

Open-label Safety Sample included all participants that had administered at least 1 dose of IMP during the open-label stabilization phase. Randomized Safety Sample included all participants who received at least 1 dose of randomized IMP during double-blind randomized withdrawal phase were included and analyzed according to the treatment received.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Open Label Stabilization Phase: Aripiprazole |
|-----------------------|--|

Reporting group description:

Participants began treatment with aripiprazole at a 2.0 mg/day dose, with the dose titrated to 5.0 mg/day after 2 days. Subsequent dose adjustments were based on the participant's weight to achieve optimum control of tics up to the maximum recommended doses based on the United States Labeling, up to Week 8 and then continued on the most stabilized dose up to minimum Week 14 or maximum Week 20. Participants who met stabilization criteria were randomized to Double-blind Randomization Phase.

|                       |   |
|-----------------------|---|
| Reporting group title | Double Blind Phase: Aripiperazole Full Dose |
|-----------------------|---|

Reporting group description:

Participants who met stabilization criteria and randomized to receive full dose of aripiprazole i.e. 5 mg or 10 mg for <50 kg participants, and 10 mg or 20 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to Week 32.

|                       |   |
|-----------------------|---|
| Reporting group title | Double Blind Phase: Aripiperazole Half Dose |
|-----------------------|---|

Reporting group description:

Participants who met stabilization criteria and randomized to receive half dose of aripiprazole i.e. 2 mg or 5 mg for <50 kg participants, and 5 mg or 10 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to Week 32.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Double Blind Phase: Placebo |
|-----------------------|-----------------------------|

Reporting group description:

Participants who met randomization criteria and randomized to receive aripiprazole matching-placebo tablets, 2 daily, orally, up to Week 32.

| Serious adverse events                            | Open Label Stabilization Phase: Aripiprazole | Double Blind Phase: Aripiperazole Full Dose | Double Blind Phase: Aripiperazole Half Dose |
|---|--|---|---|
| Total subjects affected by serious adverse events |  |   |   |
| subjects affected / exposed                       | 0 / 36 (0.00%)                               | 1 / 9 (11.11%)                              | 0 / 8 (0.00%)                               |
| number of deaths (all causes)                     | 0  | 0   | 0   |
| number of deaths resulting from adverse events    | 0  | 0   | 0   |
| Psychiatric disorders                             |  |   |   |
| Suicidal Ideation                                 |  |   |   |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 36 (0.00%) | 1 / 9 (11.11%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |

| <b>Serious adverse events</b>                     | Double Blind Phase: Placebo |  |  |
|---|-----------------------------|--|--|
| Total subjects affected by serious adverse events |                             |  |  |
| subjects affected / exposed                       | 0 / 8 (0.00%)               |  |  |
| number of deaths (all causes)                     | 0                           |  |  |
| number of deaths resulting from adverse events    | 0                           |  |  |
| Psychiatric disorders                             |                             |  |  |
| Suicidal Ideation                                 |                             |  |  |
| subjects affected / exposed                       | 0 / 8 (0.00%)               |  |  |
| occurrences causally related to treatment / all   | 0 / 0                       |  |  |
| deaths causally related to treatment / all        | 0 / 0                       |  |  |

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

| <b>Non-serious adverse events</b>                     | Open Label Stabilization Phase: Aripiprazole | Double Blind Phase: Aripiprazole Full Dose | Double Blind Phase: Aripiprazole Half Dose |
|---|--|--|--|
| Total subjects affected by non-serious adverse events |  |  |  |
| subjects affected / exposed                           | 17 / 36 (47.22%)                             | 3 / 9 (33.33%)                             | 3 / 8 (37.50%)                             |
| Investigations  |  |  |  |
| Weight increased                                      |  |  |  |
| subjects affected / exposed                           | 3 / 36 (8.33%)                               | 0 / 9 (0.00%)                              | 0 / 8 (0.00%)                              |
| occurrences (all)                                     | 3  | 0  | 0  |
| Injury, poisoning and procedural complications        |  |  |  |
| Upper limb fracture                                   |  |  |  |
| subjects affected / exposed                           | 0 / 36 (0.00%)                               | 0 / 9 (0.00%)                              | 1 / 8 (12.50%)                             |
| occurrences (all)                                     | 0  | 0  | 1  |
| Cardiac disorders                                     |  |  |  |
| Tachycardia   |  |  |  |
| subjects affected / exposed                           | 1 / 36 (2.78%)                               | 1 / 9 (11.11%)                             | 0 / 8 (0.00%)                              |
| occurrences (all)                                     | 1  | 1  | 0  |
| Nervous system disorders                              |  |  |  |
| Somnolence  |  |  |  |
| subjects affected / exposed                           | 5 / 36 (13.89%)                              | 0 / 9 (0.00%)                              | 1 / 8 (12.50%)                             |
| occurrences (all)                                     | 5  | 0  | 1  |

|  |                      |                     |                     |
|--|----------------------|---------------------|---------------------|
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 2 / 36 (5.56%)<br>4  | 0 / 9 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Sedation<br>subjects affected / exposed<br>occurrences (all)   | 4 / 36 (11.11%)<br>4 | 0 / 9 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 7 / 36 (19.44%)<br>7 | 0 / 9 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Psychiatric disorders<br>Aggression<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 36 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Enuresis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 36 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 8 (0.00%)<br>0  |
| Irritability<br>subjects affected / exposed<br>occurrences (all)   | 1 / 36 (2.78%)<br>1  | 0 / 9 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Restlessness<br>subjects affected / exposed<br>occurrences (all)   | 1 / 36 (2.78%)<br>1  | 0 / 9 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)  | 2 / 36 (5.56%)<br>2  | 0 / 9 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  |
| Infections and infestations<br>Pharyngitis streptococcal<br>subjects affected / exposed<br>occurrences (all)           | 0 / 36 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 36 (2.78%)<br>1  | 1 / 9 (11.11%)<br>1 | 0 / 8 (0.00%)<br>0  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)  | 0 / 36 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 |

| <b>Non-serious adverse events</b>  | Double Blind Phase:<br>Placebo   |  |  |
|--|--|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed   | 2 / 8 (25.00%)   |  |  |
| Investigations<br>Weight increased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0   |  |  |
| Injury, poisoning and procedural complications<br>Upper limb fracture<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0   |  |  |
| Cardiac disorders<br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0   |  |  |
| Nervous system disorders<br>Somnolence<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Sedation<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0 |  |  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0   |  |  |
| Psychiatric disorders<br>Aggression<br>subjects affected / exposed<br>occurrences (all)<br><br>Enuresis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>1<br><br>0 / 8 (0.00%)<br>0                          |  |  |

|                                   |                |  |  |
|-----------------------------------|----------------|--|--|
| Irritability                      |                |  |  |
| subjects affected / exposed       | 1 / 8 (12.50%) |  |  |
| occurrences (all)                 | 1              |  |  |
| Restlessness                      |                |  |  |
| subjects affected / exposed       | 1 / 8 (12.50%) |  |  |
| occurrences (all)                 | 1              |  |  |
| Anxiety                           |                |  |  |
| subjects affected / exposed       | 0 / 8 (0.00%)  |  |  |
| occurrences (all)                 | 0              |  |  |
| Infections and infestations       |                |  |  |
| Pharyngitis streptococcal         |                |  |  |
| subjects affected / exposed       | 0 / 8 (0.00%)  |  |  |
| occurrences (all)                 | 0              |  |  |
| Upper respiratory tract infection |                |  |  |
| subjects affected / exposed       | 0 / 8 (0.00%)  |  |  |
| occurrences (all)                 | 0              |  |  |
| Urinary tract infection           |                |  |  |
| subjects affected / exposed       | 0 / 8 (0.00%)  |  |  |
| occurrences (all)                 | 0              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 30 April 2018 | The following updates were made as per Amendment 01: Added a Week 10 visit to the double-blind phase. Allowed for remote visits (i.e., telemedicine) for selected trial visits. Decreased the number of Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS) assessments and vital signs measurements. Added waist circumference. Specified that the C-SSRS is the children's version. Added the option of micro-sampling for clinical laboratory tests. Added an interim analysis (IA). Revised language regarding sample size calculation and primary endpoint analysis. Clarified inclusion/exclusion criteria. Deleted Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) contact information in the appendices. Deleted sample assessment scales in the appendices. Updated the protocol to conform to the Otsuka template and style guide. Corrected minor typographical errors. |
| 20 June 2018  | The following updates were made as per Amendment 01: Added the EudraCT number. Increased the number of proposed sites. Specified that randomization will be stratified by region and body weight. Clarified exclusion criterion #17. Removed the option for the screening visit to be conducted remotely. Removed the option for remote visits during the open-label stabilization phase after the Week 12 visit. Clarified dose titration and specify when and how dose adjustments are permitted. Added language regarding relapse. Specified conditions for the measurement of blood pressure. Removed triplicate electrocardiograms (ECGs) so that only one ECG is done. Added details regarding Columbia-Suicide Severity Rating Scale (C-SSRS) results. Added missing clinical laboratory assessments. Corrected minor typographical errors and add clarifications to text.   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption  | Restart date |
|--------------|---|--------------|
| 30 June 2020 | This trial was terminated early due to the withdrawal of post-marketing commitment (PMC) to FDA. The planned interim analysis was not conducted either. | -            |

Notes:

### Limitations and caveats

None reported