



## Clinical trial results:

### A Randomized, Multicenter, Double-Blind, Active-Controlled, Flexible-Dose, Parallel-Group Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Symptoms of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2009-014811-11          |
| Trial protocol           | ES CZ SK Outside EU/EEA |
| Global end of trial date | 11 June 2012            |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1               |
| This version publication date  | 06 July 2016     |
| First version publication date | 05 February 2015 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | R076477PSZ3003 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01009047 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Janssen-Cilag International NV   |
| Sponsor organisation address | Antwerpseweg 15-17, B-2340 Beerse , Belgium,   |
| Public contact               | Clinical Registry Group, Janssen-Cilag International NV, +1 609-730-2436, ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Janssen-Cilag International NV, +1 609-730-2436, ClinicalTrialsEU@its.jnj.com |

Notes:

#### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000014-PIP01-07 |
| 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                       | 11 June 2012 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 11 June 2012 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 11 June 2012 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

Evaluate the efficacy of paliperidone PR relative to aripiprazole in the treatment of symptoms of schizophrenia in adolescent subjects (aged 12 to 17 years of age, inclusive) at the Week 8 endpoint as measured by the change from baseline in the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total score.

Protection of trial subjects:

The safety assessments included laboratory measurements (for example, chemistry, hematology, urinalysis, lipid panel, and insulin related tests), body weight, waist circumference, electrocardiograms (ECGs), and physical examination. The Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Rating Scale (SARS) were used to assess extrapyramidal symptoms (EPS) and dyskinesia. The Columbia Suicide Severity Rating Scale (C-SSRS) was administered to assess suicidality. Adverse events and vital signs were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 19 November 2009 |
| 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 | India: 39               |
| Country: Number of subjects enrolled | Romania: 9              |
| Country: Number of subjects enrolled | Russian Federation: 114 |
| Country: Number of subjects enrolled | Slovakia: 1             |
| Country: Number of subjects enrolled | Ukraine: 37             |
| Country: Number of subjects enrolled | United States: 22       |
| Country: Number of subjects enrolled | Spain: 5                |
| Worldwide total number of subjects   | 227                     |
| EEA total number of subjects         | 15                      |

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)                    | 0   |
| Adolescents (12-17 years)                | 227 |
| Adults (18-64 years)                     | 0   |
| From 65 to 84 years                      | 0   |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 228 subjects were included in the all randomized analysis set, 227 included in the safety analysis set and 226 in the intent-to-treat analysis set.

### Pre-assignment

Screening details:

A total of 41 sites in 7 countries participated in this study including 6 sites in India, 1 site in Romania, 16 sites in Russian Federation, 1 site in Slovakia, 3 sites in Spain, 8 sites in Ukraine, and 6 sites in the United States.

### 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:

To maintain the blind, study drug was packaged in blister cards which contained over encapsulated tablets.

### Arms

|                              |                 |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes             |
| <b>Arm title</b>             | Paliperidone ER |

Arm description:

Paliperidone extended release (ER) was administered as oral capsule at a dose of 6 milligram (mg) for 1 week and then was administered at a dose of either 3, 6 or 9 mg up to Week 26, once daily in the morning.

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Paliperidone ER |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Capsule         |
| Routes of administration               | Oral use        |

Dosage and administration details:

Paliperidone ER was administered as oral capsule at a dose of 6 milligram (mg) for 1 week and then was administered at a dose of either 3, 6 or 9 mg up to Week 26, once daily in the morning.

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

Arm description:

Aripiprazole was administered as oral capsule at a dose of 2 mg on Days 1 and 2, 5 mg on Days 3 and 4, 10 mg on Days 5, 6 and 7; and then was administered at a dose of either 5 or 10 or 15 mg up to Week 26, once daily in the morning.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Aripiprazole  |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

Aripiprazole was administered as oral capsule at a dose of 2 mg on Days 1 and 2, 5 mg on Days 3 and 4, 10 mg on Days 5, 6 and 7; and then was administered as a dose of either 5 or 10 or 15 mg up to Week 26, once daily in the morning.

| <b>Number of subjects in period 1</b> | Paliperidone ER | Aripiprazole |
|---------------------------------------|-----------------|--------------|
| Started                               | 113             | 114          |
| Completed                             | 85              | 89           |
| Not completed                         | 28              | 25           |
| Lost To Follow-Up                     | -               | 2            |
| Adverse Event                         | 5               | -            |
| Other                                 | 3               | 1            |
| Lack Of Efficacy                      | 4               | 11           |
| Withdrawal Of Consent                 | 16              | 11           |

## Baseline characteristics

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Paliperidone ER |
|-----------------------|-----------------|

Reporting group description:

Paliperidone extended release (ER) was administered as oral capsule at a dose of 6 milligram (mg) for 1 week and then was administered at a dose of either 3, 6 or 9 mg up to Week 26, once daily in the morning.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Aripiprazole |
|-----------------------|--------------|

Reporting group description:

Aripiprazole was administered as oral capsule at a dose of 2 mg on Days 1 and 2, 5 mg on Days 3 and 4, 10 on mg Days 5, 6 and 7; and then was administered at a dose of either 5 or 10 or 15 mg up to Week 26, once daily in the morning.

| Reporting group values                      | Paliperidone ER | Aripiprazole | Total |
|---|-----------------|--------------|-------|
| Number of subjects                          | 113             | 114          | 227   |
| Title for AgeCategorical<br>Units: subjects |                 |              |       |
| Children (2-11 years)                       | 0               | 0            | 0     |
| Adolescents (12-17 years)                   | 113             | 114          | 227   |
| Title for AgeContinuous<br>Units: years     |                 |              |       |
| arithmetic mean                             | 15.3            | 15.4         |       |
| standard deviation                          | ± 1.47          | ± 1.45       | -     |
| Title for Gender<br>Units: subjects         |                 |              |       |
| Female                                      | 39              | 38           | 77    |
| Male  | 74              | 76           | 150   |

## End points

### End points reporting groups

|   |                 |
|---|-----------------|
| Reporting group title   | Paliperidone ER |
| Reporting group description:<br>Paliperidone extended release (ER) was administered as oral capsule at a dose of 6 milligram (mg) for 1 week and then was administered at a dose of either 3, 6 or 9 mg up to Week 26, once daily in the morning.                         |                 |
| Reporting group title   | Aripiprazole    |
| Reporting group description:<br>Aripiprazole was administered as oral capsule at a dose of 2 mg on Days 1 and 2, 5 mg on Days 3 and 4, 10 on mg Days 5, 6 and 7; and then was administered at a dose of either 5 or 10 or 15 mg up to Week 26, once daily in the morning. |                 |

### Primary: Change From Baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score at Day 56

|  |  |
|--|--|
| End point title  | Change From Baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score at Day 56 |
| End point description:<br>The PANSS is a 30-item scale with each item rated on a scale of 1 (absent) to 7 (extreme psychopathology), designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention, and poor impulse control. The PANSS total score consists of the sum of all 30 PANSS items and ranges from 30 to 210. Higher scores indicate worsening. The intent-to-treat (ITT) population was used as analysis set which included all randomly assigned participants who received at least 1 dose of double-blind study drug, had both a Baseline measurement and at least 1 Post-Baseline measurement in the double-blind phase. Last observation carried forward (LOCF) method was used. |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline and Day 56  |  |

| End point values                     | Paliperidone ER | Aripiprazole    |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 112             | 114             |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Baseline                             | 89.6 (± 12.22)  | 92 (± 12.09)    |  |  |
| Day 56                               | -19.3 (± 13.8)  | -19.8 (± 14.56) |  |  |

### Statistical analyses

|   |                                |
|---|--------------------------------|
| Statistical analysis title  | Statistical Analysis 1         |
| Statistical analysis description:<br>Analysis of covariance (ANCOVA) model with treatment (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate was used. |                                |
| Comparison groups   | Paliperidone ER v Aripiprazole |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 226                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.935                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | L S mean difference        |
| Point estimate                          | 0.1                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -3.46                      |
| upper limit                             | 3.76                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 1.83                       |

### Secondary: Change From Baseline in PANSS Total Score at Day 182

|   |  |
|---|--|
| End point title   | Change From Baseline in PANSS Total Score at Day 182 |
| End point description:  |  |
| <p>The PANSS is a 30-item scale designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention, and poor impulse control. The 30 symptoms are rated on a 7-point scale that ranges from 1 (absent) to 7 (extreme psychopathology). The PANSS total score consists of the sum of all 30 PANSS items and ranges from 30 to 210. Higher scores indicate worsening. The ITT population included all randomly assigned participants who received at least 1 dose of double-blind study drug, had both a Baseline measurement and at least 1 Post-Baseline measurement in the double-blind phase. Last observation carried forward (LOCF) method was used.</p> |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline and Day 182  |  |

| End point values                     | Paliperidone ER | Aripiprazole    |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 112             | 114             |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Baseline                             | 89.6 (± 12.22)  | 92 (± 12.09)    |  |  |
| Change at Day 182                    | -25.6 (± 16.88) | -26.8 (± 18.82) |  |  |

### Statistical analyses

|  |                                |
|--|--------------------------------|
| Statistical analysis title   | Statistical Analysis 1         |
| Statistical analysis description:  |                                |
| <p>Analysis of covariance (ANCOVA) model with treatment groups (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate was used.</p> |                                |
| Comparison groups  | Paliperidone ER v Aripiprazole |



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 226                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.877                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | L S mean difference        |
| Point estimate                          | -0.3                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -4.68                      |
| upper limit                             | 4                          |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 2.2                        |

### Secondary: Change From Baseline in Marder Factor Negative Symptoms Score at Day 56 and 182

|   |   |
|---|---|
| End point title   | Change From Baseline in Marder Factor Negative Symptoms Score at Day 56 and 182 |
| End point description:  |   |
| The PANSS negative subscale based on marder factor assesses 7 negative-symptoms of schizophrenia. Negative symptoms represent a diminution or loss of normal functions. The symptoms are rated on a 7-point scale, with a range of 7 (absent) to 49 (extreme psychopathology). The ITT population included all randomly assigned participants who received at least 1 dose of double-blind study drug, had both a Baseline measurement and at least 1 Post-Baseline measurement in the double-blind phase. Last observation carried forward (LOCF) method was used. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Baseline, Day 56 and Day 182  |   |

| End point values                     | Paliperidone ER | Aripiprazole    |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 112             | 114             |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Baseline                             | 23.2 (± 4.92)   | 23.3 (± 4.54)   |  |  |
| Change at Day 56                     | -4.3 (± 4.56)   | -4.7 (± 4.61)   |  |  |
| Change at Day 182                    | -6 (± 5.51)     | -6.2 (± 5.84)   |  |  |

### Statistical analyses

|  |                                |
|--|--------------------------------|
| Statistical analysis title   | Statistical Analysis 1         |
| Statistical analysis description:  |                                |
| Day 56: Analysis of covariance (ANCOVA) model with treatment (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate was used. |                                |
| Comparison groups  | Paliperidone ER v Aripiprazole |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 226                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.341                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | L S mean difference        |
| Point estimate                          | 0.55                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.55                      |
| upper limit                             | 1.59                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.5                        |

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>   | Statistical Analysis 2         |
| Statistical analysis description:   |                                |
| Day 182: Analysis of covariance (ANCOVA) model with treatment (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate was used. |                                |
| Comparison groups   | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis   | 226                            |
| Analysis specification  | Pre-specified                  |
| Analysis type   | superiority                    |
| P-value   | = 0.723                        |
| Method  | ANCOVA                         |
| Parameter estimate  | LS Mean difference             |
| Point estimate  | 0.2                            |
| Confidence interval   |                                |
| level   | 95 %                           |
| sides   | 2-sided                        |
| lower limit   | -1.06                          |
| upper limit   | 1.53                           |
| Variability estimate  | Standard error of the mean     |
| Dispersion value  | 0.66                           |

## Secondary: Change From Baseline in Other Marder Factors Scores at Day 56 and 182

|   |   |
|---|---|
| End point title   | Change From Baseline in Other Marder Factors Scores at Day 56 and 182 |
| End point description:  |   |
| The subscales based on marder factors are: positive symptoms, disorganised thoughts factor, uncontrolled hostility/excitement factor, and anxiety/depression factor. The symptoms are rated on a 7-point scale, with a range of 8 to 56 for positive symptoms, 7 to 49 for disorganized thoughts and 4 to 28 for Uncontrolled hostility/excitement and anxiety/depression. Higher score indicate worsening. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Baseline, Day 56 and 182  |   |

| <b>End point values</b>                   | Paliperidone ER | Aripiprazole    |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                        | Reporting group | Reporting group |  |  |
| Number of subjects analysed               | 112             | 114             |  |  |
| Units: units on a scale                   |                 |                 |  |  |
| arithmetic mean (standard deviation)      |                 |                 |  |  |
| Baseline: Positive symptoms               | 24.6 (± 4.08)   | 24.9 (± 4.32)   |  |  |
| Change at Day 56: Positive symptoms       | -6.1 (± 4.96)   | -5.6 (± 4.83)   |  |  |
| Change at Day 182: Positive symptoms      | -7.8 (± 5.82)   | -7.8 (± 6.03)   |  |  |
| Baseline: Negative symptoms               | 23.2 (± 4.92)   | 23.3 (± 4.54)   |  |  |
| Change at Day 56: Negative symptoms       | -4.3 (± 4.56)   | -4.7 (± 4.61)   |  |  |
| Change at Day 182: Negative symptoms      | -6 (± 5.51)     | -6.2 (± 5.84)   |  |  |
| Baseline: Disorganized thoughts           | 21.4 (± 4.4)    | 22.1 (± 3.86)   |  |  |
| Change at Day 56: Disorganized thoughts   | -4 (± 3.34)     | -4.1 (± 3.4)    |  |  |
| Change at Day 182: Disorganized thoughts  | -5.5 (± 4.18)   | -5.7 (± 4.46)   |  |  |
| Baseline: Uncontrolled hostility          | 10.7 (± 3.19)   | 11.7 (± 3.48)   |  |  |
| Change at Day 56: Uncontrolled hostility  | -2.5 (± 2.67)   | -2.9 (± 3.05)   |  |  |
| Change at Day 182: Uncontrolled hostility | -3.2 (± 3.11)   | -3.8 (± 3.97)   |  |  |
| Baseline: Anxiety/depression              | 9.7 (± 3.17)    | 10 (± 3.26)     |  |  |
| Change at Day 56: Anxiety/depression      | -2.4 (± 3.08)   | -2.6 (± 2.81)   |  |  |
| Change at Day 182: Anxiety/depression     | -3 (± 3.29)     | -3.2 (± 3.17)   |  |  |

## Statistical analyses

| <b>Statistical analysis title</b> | Statistical Analysis 1 |
|-----------------------------------|------------------------|
|-----------------------------------|------------------------|

Statistical analysis description:

Change at Day 56: Positive Symptoms - ANCOVA model with treatment groups (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis | 226                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.351                        |
| Method                                  | ANCOVA                         |

| <b>Statistical analysis title</b> | Statistical Analysis 2 |
|-----------------------------------|------------------------|
|-----------------------------------|------------------------|

Statistical analysis description:

Change at Day 182: Positive Symptoms - ANCOVA model with treatment groups (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate was used.

|                   |                                |
|-------------------|--------------------------------|
| Comparison groups | Paliperidone ER v Aripiprazole |
|-------------------|--------------------------------|

|   |               |
|---|---------------|
| Number of subjects included in analysis | 226           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.691       |
| Method                                  | ANCOVA        |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Change at Day 56: Disorganized thoughts - ANCOVA model with treatment groups (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate was used.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis | 226                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.965                        |
| Method                                  | ANCOVA                         |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Change at Day 182: Disorganized thoughts - ANCOVA model with treatment groups (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate was used.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis | 226                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.766                        |
| Method                                  | ANCOVA                         |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Change at Day 56: Uncontrolled hostility/ excitement - ANCOVA model with treatment groups (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate was used.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis | 226                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.984                        |
| Method                                  | ANCOVA                         |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Change at Day 182: Uncontrolled Hostility/ Excitement - ANCOVA model with treatment groups

(paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate was used.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis | 226                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.985                        |
| Method                                  | ANCOVA                         |

|  |                                |
|--|--------------------------------|
| <b>Statistical analysis title</b>  | Statistical Analysis 7         |
| Statistical analysis description:<br>Change at Day 56: Anxiety/ depression - ANCOVA model with treatment groups (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate. |                                |
| Comparison groups  | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis  | 226                            |
| Analysis specification   | Pre-specified                  |
| Analysis type  | superiority                    |
| P-value  | = 0.803                        |
| Method   | ANCOVA                         |

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>   | Statistical Analysis 8         |
| Statistical analysis description:<br>Change at Day 182: Anxiety/ depression - ANCOVA model with treatment groups (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate. |                                |
| Comparison groups   | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis   | 226                            |
| Analysis specification  | Pre-specified                  |
| Analysis type   | superiority                    |
| P-value   | = 0.745                        |
| Method  | ANCOVA                         |

## **Secondary: Change From Baseline in Other PANSS Factors and Subscales at Day 56 and 182**

|   |   |
|---|---|
| End point title   | Change From Baseline in Other PANSS Factors and Subscales at Day 56 and 182 |
| End point description:<br>The PANSS provides a total score (sum of the scores of all 30 items) and scores for 3 subscales, the positive subscale (7 items), the negative subscale (7 items), and the general psychopathology subscale (16 items), each rated on a scale of 1 (absent) to 7 (extreme). |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline, Day 56 and 182  |   |

| End point values                           | Paliperidone ER | Aripiprazole    |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                         | Reporting group | Reporting group |  |  |
| Number of subjects analysed                | 112             | 114             |  |  |
| Units: units on a scale                    |                 |                 |  |  |
| arithmetic mean (standard deviation)       |                 |                 |  |  |
| Baseline: Positive Subscale                | 21.5 (± 4.14)   | 22.5 (± 4.26)   |  |  |
| Change at Day 56: Positive Subscale        | -6.4 (± 4.54)   | -6.2 (± 4.91)   |  |  |
| Change at Day 182: Positive Subscale       | -8 (± 5.16)     | -8.3 (± 6.09)   |  |  |
| Baseline: Negative Subscale                | 23.8 (± 4.55)   | 24.2 (± 4.32)   |  |  |
| Change at Day 56: Negative Subscale        | -4.2 (± 4.25)   | 4.5 (± 4.25)    |  |  |
| Change at Day 182: Negative Subscale       | -5.7 (± 5.15)   | -6.1 (± 5.47)   |  |  |
| Baseline: General Psychopathology          | 44.3 (± 7.47)   | 45.3 (± 7.01)   |  |  |
| Change at Day 56: General Psychopathology  | -8.7 (± 7.35)   | -9.1 (± 7.25)   |  |  |
| Change at Day 182: General Psychopathology | -11.9 (± 9.02)  | -12.4 (± 9.41)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Clinical Stability

|   |  |
|---|--|
| End point title   | Number of Participants With Clinical Stability |
| End point description:  |  |
| Clinical stability is defined as a decrease of 20 percent or more from Baseline in PANSS total score and CGI-S score less than or equal to 4 at Days 56 and 182, no hospitalizations due to psychiatric illness and no emergence of clinically significant suicidal or homicidal ideation during the maintenance phase. |  |
| End point type  | Secondary                                      |
| End point timeframe:  |  |
| Day 56 and 182  |  |

| End point values            | Paliperidone ER | Aripiprazole    |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 112             | 114             |  |  |
| Units: participants         | 58              | 68              |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| Statistical analysis title  | Statistical Analysis 1         |
| Statistical analysis description:   |                                |
| Generalized Cochran- Mantel- Haenszel test for row mean score differences controlling for country was used. |                                |
| Comparison groups   | Paliperidone ER v Aripiprazole |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 226                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.296                 |
| Method                                  | Cochran-Mantel-Haenszel |

## Secondary: Change From Baseline in Clinical Global Impression - Severity (CGI-S) Score at Days 56 and 182

|   |  |
|---|--|
| End point title   | Change From Baseline in Clinical Global Impression - Severity (CGI-S) Score at Days 56 and 182 |
| End point description:<br>The CGI-S rating scale is a 7-point global assessment that measures the Clinician's impression of the severity of illness exhibited by a participant. A rating of 1 is equivalent to "Normal, not at all ill" and a rating of 7 is equivalent to "Among the most extremely ill participants". Higher scores indicate worsening. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline, Day 56 and 182  |  |

| End point values              | Paliperidone ER | Aripiprazole    |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 112             | 114             |  |  |
| Units: units on a scale       |                 |                 |  |  |
| median (full range (min-max)) |                 |                 |  |  |
| Baseline                      | 4 (3 to 6)      | 4 (3 to 6)      |  |  |
| Change at Day 56              | -1 (-4 to 0)    | -1 (-3 to 1)    |  |  |
| Change at Day 182             | -1 (-4 to 1)    | -1 (-4 to 1)    |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| Statistical analysis title  | Statistical Analysis 1         |
| Statistical analysis description:<br>Change at Day 56: ANCOVA model on ranks with treatment groups (paliperidone ER, aripiprazole) and country as factors, and baseline value (unranked) as a covariate was used. |                                |
| Comparison groups   | Aripiprazole v Paliperidone ER |
| Number of subjects included in analysis   | 226                            |
| Analysis specification  | Pre-specified                  |
| Analysis type   | superiority                    |
| P-value   | = 0.843                        |
| Method  | ANCOVA                         |

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

**Statistical analysis description:**

Change at Day 182: ANCOVA model on ranks with treatment groups (paliperidone ER, aripiprazole) and country as factors, and baseline value (unranked) as a covariate was used.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis | 226                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.914                        |
| Method                                  | ANCOVA                         |

## Secondary: Change From Baseline in Personal and Social Performance (PSP) Scores at Day 56 and 182

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Personal and Social Performance (PSP) Scores at Day 56 and 182 |
|-----------------|--|

**End point description:**

The PSP scale assesses degree of a participants' dysfunction within 4 domains of behavior: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behavior. The results of the assessment are converted to a numerical score to rate degree of difficulty (1=absent to 6=very severe) in each of the 4 domains. Based on 4 domains there will be 1 total score (total score ranges from 1 to 100, divided into 10 equal intervals). Participants with score of 71 to 100 have mild degree of difficulty; from 31 to 70, varying degrees of disability; less than or equal to 30, functioning so poorly as to require intensive supervision.

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

**End point timeframe:**

Baseline, Day 56 and Day 182

| End point values                     | Paliperidone ER | Aripiprazole    |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 112             | 114             |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Baseline                             | 49.8 (± 10.32)  | 49.2 (± 10.21)  |  |  |
| Change at Day 56                     | 12.2 (± 11.72)  | 12.2 (± 10.17)  |  |  |
| Change at Day 182                    | 17.1 (± 14.46)  | 17.1 (± 14.03)  |  |  |

**Statistical analyses**

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 1 |
|-----------------------------------|------------------------|

**Statistical analysis description:**

Change at Day 56: Analysis of covariance (ANCOVA) model with treatment groups(paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate was used

|                   |                                |
|-------------------|--------------------------------|
| Comparison groups | Paliperidone ER v Aripiprazole |
|-------------------|--------------------------------|



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 226                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.895                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | L S mean difference        |
| Point estimate                          | 0.2                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -2.34                      |
| upper limit                             | 2.67                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 1.27                       |

|  |                                |
|--|--------------------------------|
| <b>Statistical analysis title</b>  | Statistical Analysis 2         |
| Statistical analysis description:  |                                |
| Change at Day 182: Analysis of covariance (ANCOVA) model with treatment groups (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate was used. |                                |
| Comparison groups  | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis  | 226                            |
| Analysis specification   | Pre-specified                  |
| Analysis type  | superiority                    |
| P-value  | = 0.705                        |
| Method   | ANCOVA                         |
| Parameter estimate   | L S mean difference            |
| Point estimate   | 0.6                            |
| Confidence interval  |                                |
| level  | 95 %                           |
| sides  | 2-sided                        |
| lower limit  | -2.64                          |
| upper limit  | 3.89                           |
| Variability estimate   | Standard error of the mean     |
| Dispersion value   | 1.66                           |

## Secondary: Number of Participants With PANSS Response

|  |  |
|--|--|
| End point title  | Number of Participants With PANSS Response |
| End point description:   |  |
| The PANSS is a 30-item scale with each item rated on a scale of 1 (absent) to 7 (extreme psychopathology), designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention, and poor impulse control. The PANSS total score consists of the sum of all 30 PANSS items and ranges from 30 to 210. Participants with PANSS response were defined as those who achieved greater than or equal to 20 percent or higher reduction from Baseline in the PANSS total score at Day 56 and 182. |  |
| End point type   | Secondary                                  |
| End point timeframe:   |  |
| Day 56 and 182   |  |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Paliperidone ER | Aripiprazole    |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 112             | 114             |  |  |
| Units: participants         |                 |                 |  |  |
| Day 56                      | 76              | 87              |  |  |
| Day 182                     | 86              | 93              |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>   | Statistical Analysis 1         |
| Statistical analysis description:   |                                |
| Day 56: Generalized Cochran-Mantel-Haenszel test for row mean score differences was used. |                                |
| Comparison groups   | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis   | 226                            |
| Analysis specification  | Pre-specified                  |
| Analysis type   | superiority                    |
| P-value   | = 0.119                        |
| Method  | Cochran-Mantel-Haenszel        |

|  |                                |
|--|--------------------------------|
| <b>Statistical analysis title</b>  | Statistical Analysis 2         |
| Statistical analysis description:  |                                |
| Day 182: Generalized Cochran-Mantel-Haenszel test for row mean score differences was used. |                                |
| Comparison groups  | Paliperidone ER v Aripiprazole |
| Number of subjects included in analysis  | 226                            |
| Analysis specification   | Pre-specified                  |
| Analysis type  | superiority                    |
| P-value  | = 0.444                        |
| Method   | Cochran-Mantel-Haenszel        |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 26

Adverse event reporting additional description:

The safety population included all randomly assigned participants who received at least 1 dose of double-blind study drug. A total of 113 participants in the paliperidone ER group and 114 participants in the aripiprazole group received at least 1 dose of double-blind study medication and were included in the safety analysis set.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Aripiprazole |
|-----------------------|--------------|

Reporting group description:

Aripiprazole will be administered as oral capsule at a dose of 2 mg on Days 1 and 2, 5 mg on Days 3 and 4, 10 mg Days 5, 6 and 7; and then will be administered as a dose of either 5 or 10 or 15 mg up to Week 26, once daily in the morning.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Paliperidone ER |
|-----------------------|-----------------|

Reporting group description:

Paliperidone ER will be administered as oral capsule at a dose of 6 milligram (mg) for 1 week and then will be administered at a dose of either 3, 6 or 9 mg up to Week 26, once daily in the morning.

| Serious adverse events                            | Aripiprazole    | Paliperidone ER |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 7 / 114 (6.14%) | 7 / 113 (6.19%) |  |
| number of deaths (all causes)                     | 0               | 0               |  |
| number of deaths resulting from adverse events    | 0               | 0               |  |
| Psychiatric disorders                             |                 |                 |  |
| Agitation   |                 |                 |  |
| subjects affected / exposed                       | 1 / 114 (0.88%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Anxiety   |                 |                 |  |
| subjects affected / exposed                       | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Psychotic disorder                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 114 (0.88%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Schizophrenia                                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 114 (3.51%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Schizophrenia, paranoid type                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Suicide attempt                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Sinusitis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| Non-serious adverse events                            | Aripiprazole      | Paliperidone ER   |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 75 / 114 (65.79%) | 87 / 113 (76.99%) |  |
| Vascular disorders                                    |                   |                   |  |
| Orthostatic hypotension                               |                   |                   |  |
| subjects affected / exposed                           | 0 / 114 (0.00%)   | 1 / 113 (0.88%)   |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| General disorders and administration                  |                   |                   |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| site conditions                          |                 |                 |  |
| Asthenia                                 |                 |                 |  |
| subjects affected / exposed              | 1 / 114 (0.88%) | 6 / 113 (5.31%) |  |
| occurrences (all)                        | 1               | 7               |  |
| Fatigue                                  |                 |                 |  |
| subjects affected / exposed              | 2 / 114 (1.75%) | 1 / 113 (0.88%) |  |
| occurrences (all)                        | 2               | 2               |  |
| Feeling jittery                          |                 |                 |  |
| subjects affected / exposed              | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences (all)                        | 1               | 0               |  |
| Gait disturbance                         |                 |                 |  |
| subjects affected / exposed              | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)                        | 0               | 1               |  |
| Irritability                             |                 |                 |  |
| subjects affected / exposed              | 1 / 114 (0.88%) | 1 / 113 (0.88%) |  |
| occurrences (all)                        | 1               | 1               |  |
| Malaise                                  |                 |                 |  |
| subjects affected / exposed              | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)                        | 0               | 1               |  |
| Pyrexia                                  |                 |                 |  |
| subjects affected / exposed              | 1 / 114 (0.88%) | 2 / 113 (1.77%) |  |
| occurrences (all)                        | 1               | 2               |  |
| Thirst                                   |                 |                 |  |
| subjects affected / exposed              | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)                        | 0               | 1               |  |
| Social circumstances                     |                 |                 |  |
| Sexual activity increased                |                 |                 |  |
| subjects affected / exposed              | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences (all)                        | 1               | 0               |  |
| Reproductive system and breast disorders |                 |                 |  |
| Amenorrhoea                              |                 |                 |  |
| subjects affected / exposed              | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)                        | 0               | 1               |  |
| Epididymitis                             |                 |                 |  |
| subjects affected / exposed              | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences (all)                        | 1               | 0               |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Erectile dysfunction<br>subjects affected / exposed<br>occurrences (all)   | 0 / 114 (0.00%)<br>0 | 1 / 113 (0.88%)<br>1 |  |
| Galactorrhoea<br>subjects affected / exposed<br>occurrences (all)          | 1 / 114 (0.88%)<br>1 | 2 / 113 (1.77%)<br>3 |  |
| Gynaecomastia<br>subjects affected / exposed<br>occurrences (all)          | 0 / 114 (0.00%)<br>0 | 1 / 113 (0.88%)<br>1 |  |
| Menstruation irregular<br>subjects affected / exposed<br>occurrences (all) | 0 / 114 (0.00%)<br>0 | 1 / 113 (0.88%)<br>1 |  |
| Respiratory, thoracic and mediastinal disorders                            |                      |                      |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)       | 0 / 114 (0.00%)<br>0 | 1 / 113 (0.88%)<br>1 |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)     | 0 / 114 (0.00%)<br>0 | 2 / 113 (1.77%)<br>2 |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)            | 0 / 114 (0.00%)<br>0 | 1 / 113 (0.88%)<br>1 |  |
| Sinus congestion<br>subjects affected / exposed<br>occurrences (all)       | 1 / 114 (0.88%)<br>1 | 0 / 113 (0.00%)<br>0 |  |
| Psychiatric disorders  |                      |                      |  |
| Aggression<br>subjects affected / exposed<br>occurrences (all)             | 0 / 114 (0.00%)<br>0 | 1 / 113 (0.88%)<br>1 |  |
| Abnormal dreams<br>subjects affected / exposed<br>occurrences (all)        | 1 / 114 (0.88%)<br>1 | 1 / 113 (0.88%)<br>1 |  |
| Agitation<br>subjects affected / exposed<br>occurrences (all)              | 2 / 114 (1.75%)<br>2 | 1 / 113 (0.88%)<br>1 |  |
| Anxiety  |                      |                      |  |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 114 (2.63%) | 5 / 113 (4.42%) |
| occurrences (all)           | 3               | 6               |
| Depression                  |                 |                 |
| subjects affected / exposed | 2 / 114 (1.75%) | 3 / 113 (2.65%) |
| occurrences (all)           | 2               | 4               |
| Dyssomnia                   |                 |                 |
| subjects affected / exposed | 1 / 114 (0.88%) | 0 / 113 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Hallucination               |                 |                 |
| subjects affected / exposed | 0 / 114 (0.00%) | 2 / 113 (1.77%) |
| occurrences (all)           | 0               | 3               |
| Hostility                   |                 |                 |
| subjects affected / exposed | 1 / 114 (0.88%) | 0 / 113 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Libido decreased            |                 |                 |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%) |
| occurrences (all)           | 0               | 1               |
| Insomnia                    |                 |                 |
| subjects affected / exposed | 9 / 114 (7.89%) | 6 / 113 (5.31%) |
| occurrences (all)           | 12              | 9               |
| Mood swings                 |                 |                 |
| subjects affected / exposed | 1 / 114 (0.88%) | 0 / 113 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Nervousness                 |                 |                 |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%) |
| occurrences (all)           | 0               | 1               |
| Nightmare                   |                 |                 |
| subjects affected / exposed | 1 / 114 (0.88%) | 0 / 113 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Psychogenic pain disorder   |                 |                 |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%) |
| occurrences (all)           | 0               | 1               |
| Restlessness                |                 |                 |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%) |
| occurrences (all)           | 0               | 1               |
| Psychotic disorder          |                 |                 |

|  |                  |                 |  |
|--|------------------|-----------------|--|
| subjects affected / exposed            | 0 / 114 (0.00%)  | 1 / 113 (0.88%) |  |
| occurrences (all)                      | 0                | 1               |  |
| Schizophrenia                          |                  |                 |  |
| subjects affected / exposed            | 10 / 114 (8.77%) | 3 / 113 (2.65%) |  |
| occurrences (all)                      | 12               | 5               |  |
| Sleep disorder                         |                  |                 |  |
| subjects affected / exposed            | 1 / 114 (0.88%)  | 0 / 113 (0.00%) |  |
| occurrences (all)                      | 1                | 0               |  |
| Social avoidant behaviour              |                  |                 |  |
| subjects affected / exposed            | 0 / 114 (0.00%)  | 1 / 113 (0.88%) |  |
| occurrences (all)                      | 0                | 1               |  |
| Suicidal ideation                      |                  |                 |  |
| subjects affected / exposed            | 0 / 114 (0.00%)  | 2 / 113 (1.77%) |  |
| occurrences (all)                      | 0                | 2               |  |
| Suicide attempt                        |                  |                 |  |
| subjects affected / exposed            | 0 / 114 (0.00%)  | 1 / 113 (0.88%) |  |
| occurrences (all)                      | 0                | 1               |  |
| Investigations                         |                  |                 |  |
| Alanine aminotransferase increased     |                  |                 |  |
| subjects affected / exposed            | 0 / 114 (0.00%)  | 1 / 113 (0.88%) |  |
| occurrences (all)                      | 0                | 1               |  |
| Aspartate aminotransferase increased   |                  |                 |  |
| subjects affected / exposed            | 1 / 114 (0.88%)  | 1 / 113 (0.88%) |  |
| occurrences (all)                      | 1                | 1               |  |
| Blood creatine phosphokinase increased |                  |                 |  |
| subjects affected / exposed            | 0 / 114 (0.00%)  | 1 / 113 (0.88%) |  |
| occurrences (all)                      | 0                | 1               |  |
| Blood glucose                          |                  |                 |  |
| subjects affected / exposed            | 1 / 114 (0.88%)  | 0 / 113 (0.00%) |  |
| occurrences (all)                      | 1                | 0               |  |
| Blood triglycerides increased          |                  |                 |  |
| subjects affected / exposed            | 1 / 114 (0.88%)  | 0 / 113 (0.00%) |  |
| occurrences (all)                      | 1                | 0               |  |
| Electrocardiogram QT prolonged         |                  |                 |  |



|  |                 |                   |  |
|--|-----------------|-------------------|--|
| subjects affected / exposed                    | 2 / 114 (1.75%) | 0 / 113 (0.00%)   |  |
| occurrences (all)                              | 2               | 0                 |  |
| Gastric pH decreased                           |                 |                   |  |
| subjects affected / exposed                    | 0 / 114 (0.00%) | 1 / 113 (0.88%)   |  |
| occurrences (all)                              | 0               | 1                 |  |
| Hepatic enzyme increased                       |                 |                   |  |
| subjects affected / exposed                    | 0 / 114 (0.00%) | 1 / 113 (0.88%)   |  |
| occurrences (all)                              | 0               | 1                 |  |
| Weight decreased                               |                 |                   |  |
| subjects affected / exposed                    | 3 / 114 (2.63%) | 0 / 113 (0.00%)   |  |
| occurrences (all)                              | 4               | 0                 |  |
| High density lipoprotein decreased             |                 |                   |  |
| subjects affected / exposed                    | 0 / 114 (0.00%) | 1 / 113 (0.88%)   |  |
| occurrences (all)                              | 0               | 1                 |  |
| Weight increased                               |                 |                   |  |
| subjects affected / exposed                    | 7 / 114 (6.14%) | 12 / 113 (10.62%) |  |
| occurrences (all)                              | 7               | 14                |  |
| Injury, poisoning and procedural complications |                 |                   |  |
| Contusion                                      |                 |                   |  |
| subjects affected / exposed                    | 0 / 114 (0.00%) | 2 / 113 (1.77%)   |  |
| occurrences (all)                              | 0               | 2                 |  |
| Cardiac disorders                              |                 |                   |  |
| Sinus tachycardia                              |                 |                   |  |
| subjects affected / exposed                    | 0 / 114 (0.00%) | 1 / 113 (0.88%)   |  |
| occurrences (all)                              | 0               | 1                 |  |
| Tachycardia                                    |                 |                   |  |
| subjects affected / exposed                    | 2 / 114 (1.75%) | 3 / 113 (2.65%)   |  |
| occurrences (all)                              | 3               | 4                 |  |
| Ventricular extrasystoles                      |                 |                   |  |
| subjects affected / exposed                    | 0 / 114 (0.00%) | 1 / 113 (0.88%)   |  |
| occurrences (all)                              | 0               | 1                 |  |
| Nervous system disorders                       |                 |                   |  |
| Akathisia                                      |                 |                   |  |
| subjects affected / exposed                    | 9 / 114 (7.89%) | 13 / 113 (11.50%) |  |
| occurrences (all)                              | 10              | 13                |  |
| Disturbance in attention                       |                 |                   |  |

|                             |                 |                   |
|-----------------------------|-----------------|-------------------|
| subjects affected / exposed | 1 / 114 (0.88%) | 0 / 113 (0.00%)   |
| occurrences (all)           | 1               | 0                 |
| Dizziness                   |                 |                   |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%)   |
| occurrences (all)           | 0               | 1                 |
| Dysarthria                  |                 |                   |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%)   |
| occurrences (all)           | 0               | 1                 |
| Droling                     |                 |                   |
| subjects affected / exposed | 2 / 114 (1.75%) | 0 / 113 (0.00%)   |
| occurrences (all)           | 2               | 0                 |
| Dyskinesia                  |                 |                   |
| subjects affected / exposed | 1 / 114 (0.88%) | 1 / 113 (0.88%)   |
| occurrences (all)           | 1               | 1                 |
| Dystonia                    |                 |                   |
| subjects affected / exposed | 3 / 114 (2.63%) | 1 / 113 (0.88%)   |
| occurrences (all)           | 3               | 1                 |
| Extrapyramidal disorder     |                 |                   |
| subjects affected / exposed | 2 / 114 (1.75%) | 3 / 113 (2.65%)   |
| occurrences (all)           | 2               | 3                 |
| Grimacing                   |                 |                   |
| subjects affected / exposed | 1 / 114 (0.88%) | 0 / 113 (0.00%)   |
| occurrences (all)           | 1               | 0                 |
| Headache                    |                 |                   |
| subjects affected / exposed | 5 / 114 (4.39%) | 12 / 113 (10.62%) |
| occurrences (all)           | 6               | 18                |
| Hypersomnia                 |                 |                   |
| subjects affected / exposed | 0 / 114 (0.00%) | 2 / 113 (1.77%)   |
| occurrences (all)           | 0               | 2                 |
| Lethargy                    |                 |                   |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%)   |
| occurrences (all)           | 0               | 2                 |
| Hypokinesia                 |                 |                   |
| subjects affected / exposed | 1 / 114 (0.88%) | 0 / 113 (0.00%)   |
| occurrences (all)           | 1               | 0                 |
| Paraesthesia                |                 |                   |

|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 114 (0.00%)<br>0    | 1 / 113 (0.88%)<br>1    |  |
| Parkinsonism<br>subjects affected / exposed<br>occurrences (all)                                    | 3 / 114 (2.63%)<br>4    | 2 / 113 (1.77%)<br>2    |  |
| Psychomotor hyperactivity<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 114 (0.88%)<br>2    | 0 / 113 (0.00%)<br>0    |  |
| Sedation<br>subjects affected / exposed<br>occurrences (all)  | 3 / 114 (2.63%)<br>4    | 6 / 113 (5.31%)<br>6    |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)  | 11 / 114 (9.65%)<br>12  | 12 / 113 (10.62%)<br>13 |  |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)                                      | 12 / 114 (10.53%)<br>13 | 12 / 113 (10.62%)<br>14 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 114 (0.88%)<br>1    | 0 / 113 (0.00%)<br>0    |  |
| Eosinophilia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 114 (0.00%)<br>0    | 1 / 113 (0.88%)<br>1    |  |
| Monocytopenia<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 114 (0.88%)<br>1    | 0 / 113 (0.00%)<br>0    |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)          | 1 / 114 (0.88%)<br>2    | 5 / 113 (4.42%)<br>7    |  |
| Eye disorders<br>Accommodation disorder<br>subjects affected / exposed<br>occurrences (all)         | 1 / 114 (0.88%)<br>2    | 0 / 113 (0.00%)<br>0    |  |
| Blepharospasm   |                         |                         |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Eye pruritus                |                 |                 |  |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Lacrimation increased       |                 |                 |  |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Oculogyric crisis           |                 |                 |  |
| subjects affected / exposed | 0 / 114 (0.00%) | 3 / 113 (2.65%) |  |
| occurrences (all)           | 0               | 4               |  |
| Photophobia                 |                 |                 |  |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Vision blurred              |                 |                 |  |
| subjects affected / exposed | 0 / 114 (0.00%) | 3 / 113 (2.65%) |  |
| occurrences (all)           | 0               | 3               |  |
| Gastrointestinal disorders  |                 |                 |  |
| Abdominal pain              |                 |                 |  |
| subjects affected / exposed | 1 / 114 (0.88%) | 1 / 113 (0.88%) |  |
| occurrences (all)           | 1               | 1               |  |
| Abdominal pain upper        |                 |                 |  |
| subjects affected / exposed | 2 / 114 (1.75%) | 0 / 113 (0.00%) |  |
| occurrences (all)           | 2               | 0               |  |
| Constipation                |                 |                 |  |
| subjects affected / exposed | 0 / 114 (0.00%) | 2 / 113 (1.77%) |  |
| occurrences (all)           | 0               | 3               |  |
| Diarrhoea                   |                 |                 |  |
| subjects affected / exposed | 2 / 114 (1.75%) | 1 / 113 (0.88%) |  |
| occurrences (all)           | 2               | 1               |  |
| Dyspepsia                   |                 |                 |  |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Eructation                  |                 |                 |  |
| subjects affected / exposed | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Flatulence                             |                 |                 |  |
| subjects affected / exposed            | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)                      | 0               | 1               |  |
| Nausea                                 |                 |                 |  |
| subjects affected / exposed            | 7 / 114 (6.14%) | 4 / 113 (3.54%) |  |
| occurrences (all)                      | 8               | 4               |  |
| Salivary hypersecretion                |                 |                 |  |
| subjects affected / exposed            | 2 / 114 (1.75%) | 5 / 113 (4.42%) |  |
| occurrences (all)                      | 2               | 6               |  |
| Tongue disorder                        |                 |                 |  |
| subjects affected / exposed            | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)                      | 0               | 1               |  |
| Toothache                              |                 |                 |  |
| subjects affected / exposed            | 1 / 114 (0.88%) | 1 / 113 (0.88%) |  |
| occurrences (all)                      | 1               | 1               |  |
| Vomiting                               |                 |                 |  |
| subjects affected / exposed            | 1 / 114 (0.88%) | 8 / 113 (7.08%) |  |
| occurrences (all)                      | 1               | 9               |  |
| Skin and subcutaneous tissue disorders |                 |                 |  |
| Acne                                   |                 |                 |  |
| subjects affected / exposed            | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)                      | 0               | 1               |  |
| Alopecia                               |                 |                 |  |
| subjects affected / exposed            | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences (all)                      | 0               | 1               |  |
| Dermatitis                             |                 |                 |  |
| subjects affected / exposed            | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences (all)                      | 1               | 0               |  |
| Dermatitis allergic                    |                 |                 |  |
| subjects affected / exposed            | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences (all)                      | 1               | 0               |  |
| Hyperhidrosis                          |                 |                 |  |
| subjects affected / exposed            | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences (all)                      | 2               | 0               |  |
| Pruritus                               |                 |                 |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 114 (0.88%)<br>1 | 0 / 113 (0.00%)<br>0 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 0 / 114 (0.00%)<br>0 | 1 / 113 (0.88%)<br>2 |  |
| Seborrhoea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 114 (0.88%)<br>1 | 0 / 113 (0.00%)<br>0 |  |
| Seborrhoeic dermatitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 114 (0.88%)<br>1 | 0 / 113 (0.00%)<br>0 |  |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 114 (0.00%)<br>0 | 1 / 113 (0.88%)<br>1 |  |
| Musculoskeletal and connective tissue disorders<br>Arthritis reactive<br>subjects affected / exposed<br>occurrences (all) | 0 / 114 (0.00%)<br>0 | 1 / 113 (0.88%)<br>1 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 114 (0.00%)<br>0 | 2 / 113 (1.77%)<br>3 |  |
| Muscle rigidity<br>subjects affected / exposed<br>occurrences (all)   | 3 / 114 (2.63%)<br>4 | 7 / 113 (6.19%)<br>8 |  |
| Muscle tightness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 114 (0.00%)<br>0 | 2 / 113 (1.77%)<br>2 |  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 114 (0.88%)<br>1 | 0 / 113 (0.00%)<br>0 |  |
| Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all)   | 1 / 114 (0.88%)<br>1 | 1 / 113 (0.88%)<br>1 |  |
| Trismus   |                      |                      |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 114 (0.00%)<br>0 | 1 / 113 (0.88%)<br>1 |  |
| Infections and infestations                      |                      |                      |  |
| Acute sinusitis                                  |                      |                      |  |
| subjects affected / exposed                      | 1 / 114 (0.88%)      | 0 / 113 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Bronchitis                                       |                      |                      |  |
| subjects affected / exposed                      | 1 / 114 (0.88%)      | 2 / 113 (1.77%)      |  |
| occurrences (all)                                | 1                    | 2                    |  |
| Cystitis   |                      |                      |  |
| subjects affected / exposed                      | 1 / 114 (0.88%)      | 0 / 113 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Gastroenteritis viral                            |                      |                      |  |
| subjects affected / exposed                      | 0 / 114 (0.00%)      | 1 / 113 (0.88%)      |  |
| occurrences (all)                                | 0                    | 1                    |  |
| Hordeolum  |                      |                      |  |
| subjects affected / exposed                      | 1 / 114 (0.88%)      | 0 / 113 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Influenza  |                      |                      |  |
| subjects affected / exposed                      | 2 / 114 (1.75%)      | 1 / 113 (0.88%)      |  |
| occurrences (all)                                | 2                    | 1                    |  |
| Nasopharyngitis                                  |                      |                      |  |
| subjects affected / exposed                      | 5 / 114 (4.39%)      | 5 / 113 (4.42%)      |  |
| occurrences (all)                                | 5                    | 6                    |  |
| Respiratory tract infection                      |                      |                      |  |
| subjects affected / exposed                      | 2 / 114 (1.75%)      | 0 / 113 (0.00%)      |  |
| occurrences (all)                                | 2                    | 0                    |  |
| Respiratory tract infection viral                |                      |                      |  |
| subjects affected / exposed                      | 0 / 114 (0.00%)      | 1 / 113 (0.88%)      |  |
| occurrences (all)                                | 0                    | 1                    |  |
| Sinusitis  |                      |                      |  |
| subjects affected / exposed                      | 1 / 114 (0.88%)      | 0 / 113 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Tonsillitis                                      |                      |                      |  |
| subjects affected / exposed                      | 2 / 114 (1.75%)      | 0 / 113 (0.00%)      |  |
| occurrences (all)                                | 2                    | 0                    |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Tooth abscess<br>subjects affected / exposed<br>occurrences (all)  | 0 / 114 (0.00%)<br>0 | 1 / 113 (0.88%)<br>1 |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 114 (0.88%)<br>1 | 1 / 113 (0.88%)<br>1 |  |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 114 (0.88%)<br>1 | 1 / 113 (0.88%)<br>1 |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 6 / 114 (5.26%)<br>6 | 2 / 113 (1.77%)<br>2 |  |
| Glucose tolerance impaired<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 114 (0.00%)<br>0 | 2 / 113 (1.77%)<br>2 |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 114 (0.88%)<br>1 | 0 / 113 (0.00%)<br>0 |  |
| Impaired fasting glucose<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 114 (0.00%)<br>0 | 2 / 113 (1.77%)<br>2 |  |
| Increased appetite<br>subjects affected / exposed<br>occurrences (all)                                       | 2 / 114 (1.75%)<br>3 | 2 / 113 (1.77%)<br>2 |  |



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported