# Clinical trial results:
# A Phase 3, Long-term, Open-label Study of Istradefylline in Subjects with Moderate to Severe Parkinson's Disease

## Summary

| | |
|---|---|
| EudraCT number | 2015-003887-34 |
| Trial protocol | DE CZ PL IT |
| Global end of trial date | 20 December 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 03 January 2019 |
| First version publication date | 03 January 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 6002-018 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02610231 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Kyowa Kirin Pharmaceutical Development, Inc |
| Sponsor organisation address | 212 Carnegie Center, Princeton, United States, 08540 |
| Public contact | Clinical Trial Help Desk, Kyowa Kirin Pharmaceutical Development, Inc., 6002014helpdesk@kyowakirin.com |
| Scientific contact | Clinical Trial Help Desk, Kyowa Kirin Pharmaceutical Development, Inc., 6002014helpdesk@kyowakirin.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 08 February 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 December 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 December 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of oral istradefylline 20 to 40 mg/d as treatment for subjects with moderate to severe Parkinson's Disease (PD).

Protection of trial subjects:

The Principal Investigators were responsible for the conduct and administration of the study in accordance with the protocol and ICH E6-GCP (CPMP/ICH/135/95) guidelines, for collecting, recording, and reporting the data accurately and properly as well as compliance with 21CFR Parts 11, 50,54,56 and 312 and the applicable country -specific requirements and in accordance with the ethical principles enunciated in the Declaration of Helsinki adopted by the 18th World Medical Association (WMA) General Assembly in Helsinki, Finland (June 1964); and amended most recently in 2013 (ninth revision). The Principal Investigator at each center was also responsible for contacts with study center management, the IEC/IRB, and with local non-regulatory bodies. Agreement of the Investigator to conduct and administer this study in accordance with the protocol was documented in separate study agreements with the Sponsor and other forms as required by national authorities in the country where the study center was located. The Informed Consent Form (ICF) incorporated the required elements for informed consent, including the possible treatment risks and necessary documentation as required by the Declaration of Helsinki, 21 CFR Part 50, and the ICH-GCP (CPMP/ICH/135/95) guidelines. The ICF also contained any additional information required by local laws relating to IRB/IEC review. The ICF was approved by the IRB/IEC and the Sponsor. The subject's willingness to participate in the study was documented in writing (signed and dated by the subject [or by the subject's legally acceptable representative] and by the person who conducted the informed consent discussion). The Investigators kept the original consent forms and copies were given to the subjects. No procedures were to take place until ICF was signed.

Background therapy:

The study was an open-label, phase 3 continuation of study 6002-014 for the long term extension of treatment up to 52 weeks. Subjects must have completed 12 weeks of double blind treatment and a 30 day follow up period prior to enrollment in 6002-018.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 18 February 2016 |
| 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 | Poland: 49 |
| Country: Number of subjects enrolled | Germany: 12 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | United States: 79 |
| Country: Number of subjects enrolled | Serbia: 18 |
| Country: Number of subjects enrolled | Israel: 16 |

| | |
|---|---|
| Country: Number of subjects enrolled | Italy: 18 |
| Country: Number of subjects enrolled | Czech Republic: 41 |
| Worldwide total number of subjects | 239 |
| EEA total number of subjects | 120 |

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) | 0 |
| Adults (18-64 years) | 109 |
| From 65 to 84 years | 129 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment opened in February 2016 and closed 16 November 2016.

### Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects that met all the inclusion/exclusion criteria as per the protocol, were eligible for entry into the trial. A total of 243 subjects were enrolled (screened) of which 4 failed. 239 subjects were therefore enrolled into the trial.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Overall Trial |

Arm description:

Open label study therefore all subjects were treated with istradefylline at a starting dose of 20 mg/d with an option for a dose adjustment to 40 mg/d at week 12 based on the Investigator's judgement of each subject's response and tolerability.

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

Dosage and administration details:

Subjects were treated with istradefylline at a starting dose of 20 mg/d with an option for a dose adjustment to 40 mg/d at week 12 based on the Investigator's judgement of each subject's response and tolerability. If deemed necessary, one unscheduled dose adjustment dose adjustment visit between weeks 2 and 12 was allowed in accordance with the Investigator's clinical judgement. Subject's who had a dose adjustment to 40mg/d could have their their dose decreased to 20mg/d by the investigator at a second unscheduled dose adjustment visit if there were tolerability issues. The istradefylline dose was to remain fixed between weeks 26 and 52. Consultation with the Sponsors Medical Monitor was required prior to any unscheduled dose adjustment visits. Study drug was to be taken in the morning for the duration of study participation on an outpatient basis. Study drug could be taken with or without food.

| **Number of subjects in period 1** | Overall Trial |
|---|---|
| Started | 239 |
| Week 12 | 219 |
| Week 26 | 198 |
| Completed | 179 |
| Not completed | 60 |
| Adverse event, serious fatal | 5 |
| Consent withdrawn by subject | 27 |

| | |
|---|---|
| Physician decision | 1 |
| Adverse event, non-fatal | 20 |
| Unknown | 3 |
| Non-compliance | 2 |
| Surgery | 2 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall Trial |
|---|---|

Reporting group description: -

| Reporting group values | Overall Trial | Total | |
|---|---|---|---|
| Number of subjects | 239 | 239 | |
| Age categorical | | | |
| Due to change in German Privacy Law the age for two subjects was not entered. The age of these subjects were estimated in the enrolled reporting table but have been added as unknown to the age categorical table. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 108 | 108 | |
| From 65-84 years | 128 | 128 | |
| 85 years and over | 1 | 1 | |
| Unknown (age not collected) | 2 | 2 | |
| Age continuous | | | |
| Due to change in German Privacy Law the age for two subjects was not entered. The age of these subjects were estimated in the enrolled reporting table but have been added as unknown to the age continuous table. | | | |
| Units: years | | | |
| arithmetic mean | 65.0 | | |
| standard deviation | ± 8.95 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 87 | 87 | |
| Male | 152 | 152 | |

### Subject analysis sets

| Subject analysis set title | Efficacy analysis |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Efficacy analyses were based on the Intent to treat population, defined as all subjects who had both a valid baseline and at least one valid post-baseline efficacy assessment.

| Subject analysis set title | Safety Evaluation |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Safety analysis was based on the safety analysis set. All continuous safety data that was collected in the study was summarized using descriptive statistics at each assessment time based on actual values and change from baseline values.

| **Reporting group values** | Efficacy analysis | Safety Evaluation | |
|---|---|---|---|
| Number of subjects | 238 | 239 | |
| Age categorical | | | |
| Due to change in German Privacy Law the age for two subjects was not entered. The age of these subjects were estimated in the enrolled reporting table but have been added as unknown to the age categorical table. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 107 | 108 | |
| From 65-84 years | 128 | 128 | |
| 85 years and over | 1 | 1 | |
| Unknown (age not collected) | 2 | 2 | |
| Age continuous | | | |
| Due to change in German Privacy Law the age for two subjects was not entered. The age of these subjects were estimated in the enrolled reporting table but have been added as unknown to the age continuous table. | | | |
| Units: years | | | |
| arithmetic mean | 65 | 65 | |
| standard deviation | ± 8.96 | ± 8.95 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 86 | 87 | |
| Male | 152 | 152 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Overall Trial |

Reporting group description:

Open label study therefore all subjects were treated with istradefylline at a starting dose of 20 mg/d with an option for a dose adjustment to 40 mg/d at week 12 based on the Investigator's judgement of each subject's response and tolerability.

| | |
|---|---|
| Subject analysis set title | Efficacy analysis |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Efficacy analyses were based on the Intent to treat population, defined as all subjects who had both a valid baseline and at least one valid post-baseline efficacy assessment.

| | |
|---|---|
| Subject analysis set title | Safety Evaluation |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Safety analysis was based on the safety analysis set. All continuous safety data that was collected in the study was summarized using descriptive statistics at each assessment time based on actual values and change from baseline values.

### Primary: Safety Analysis based on the Safety Analysis Set.

| | |
|---|---|
| End point title | Safety Analysis based on the Safety Analysis Set.[1] |

End point description:

All continuous safety data collected in this study was categorised using descriptive statistics at each assessment time based on actual values and change from baseline values.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

From the time ICF was signed through to 30 days post last dose administration.

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: Statistical Analysis was performed using descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum) for continuous variables and frequency distributions and percentages for discrete (or any categorical) variables were utilized.

| End point values | Overall Trial | Safety Evaluation | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 239 | 239 | | |
| Units: Adverse events | | | | |
| Subjects with any TEAE | 141 | 141 | | |
| Subjects with any serious TEAE | 30 | 30 | | |
| Subjects with any TEAE leading to discontinuation | 25 | 25 | | |
| Subjects with any related TEAE | 78 | 78 | | |
| Subjects with any severe TEAE | 27 | 27 | | |
| Subjects who died | 5 | 5 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Efficacy Analysis based on the PGI-I scores at end of study (Week 52) as a percentage

| End point title | Efficacy Analysis based on the PGI-I scores at end of study (Week 52) as a percentage |
|---|---|

End point description:

The percentage of subjects showing improvement (moderate and mild) at week 52.

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

End point timeframe:

From baseline to week 52 (end of study)

| End point values | Efficacy analysis | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 187 | | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Overall Condition | 40.7 | | | |
| Fatigue | 21.4 | | | |
| Sleep | 19.8 | | | |
| Motivation to get things done | 24.1 | | | |
| Key Symptom | 39 | | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time the subject signs the ICF and until 30 days after last dose of study drug.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Safety Evaluation |

Reporting group description:

All safety analyses was based on the safety analyses set. All continuous safety data collected in this study was summarized using descriptive statistics at each assessment time based on actual values and changes from baseline values. Baseline was defined as the last non missing value obtained prior to first treatment. Continuous variables were summarized using n, mean, SD, median,minimum, and maximum values. Categorical variables were summarized using the number and percentage of subjects in each category. All out of normal range results and clinically significant changes in any safety variable were flagged in the subject data listings.

| **Serious adverse events** | Safety Evaluation | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 30 / 239 (12.55%) | | |
| number of deaths (all causes) | 5 | | |
| number of deaths resulting from adverse events | 5 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Panic attack | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Protein total decreased | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Limb amputation | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Procedural pain | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pubis fracture | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Incorrect dose administered | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fall | | | | |
| subjects affected / exposed | 3 / 239 (1.26%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femur fracture | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorders | | | | |
| Coronary artery disease | | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac arrest | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrioventricular block complete | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Nervous system disorders | | | |
| On and off phenomenon | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Parkinson's disease | | | |
| subjects affected / exposed | 3 / 239 (1.26%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Convulsion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple sclerosis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyskinesia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Glaucoma | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diplopia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal column stenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Gas gangrene | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Safety Evaluation | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 87 / 239 (36.40%) | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 27 / 239 (11.30%) | | |
| occurrences (all) | 37 | | |
| Nervous system disorders | | | |
| Dyskinesia | | | |
| subjects affected / exposed | 42 / 239 (17.57%) | | |
| occurrences (all) | 50 | | |
| Parkinson's disease | | | |
| subjects affected / exposed | 18 / 239 (7.53%) | | |
| occurrences (all) | 21 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported