

**Clinical trial results:**

Efficacy and safety of BIA 9-1067 in idiopathic Parkinson's disease patients with "wearing-off" phenomenon treated with levodopa plus a dopa decarboxylase inhibitor (ddci): a double blind, randomised, placebo- and active-controlled, parallel group, multicentre clinical study

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2010-021860-13 |
| Trial protocol | HU LT AT LV DE ES PT CZ SK BG RO IT |
| Global end of trial date | 01 December 2014 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 22 July 2016 |
| First version publication date | 19 March 2016 |
| Version creation reason | |
| Summary attachment (see zip file) | BIA-91067-301_Synopsis_DB (BIA-91067-301_Synopsis_DB.pdf) BIA-91067-301_Synopsis_OL (BIA-91067-301_Synopsis_OL.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|---------------|
| Sponsor protocol code | BIA-91067-301 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01568073 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | BIAL - Portela & CA, S.A. |
| Sponsor organisation address | À Av. Siderurgia Nacional, Coronado, Portugal, 4745-457 |
| Public contact | André Garrido, BIAL - Portela & Cª, S.A., 0035 229866100, andre.garrido@bial.com |
| Scientific contact | José Francisco Rocha, BIAL - Portela & Cª, S.A., 0035 229866100, jose.rocha@bial.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 | 21 April 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 November 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 December 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary: To investigate the efficacy of 3 different doses of BIA 9-1067 (5 mg, 25 mg, and 50 mg) administered once a day, compared with 200 mg of entacapone or placebo, when administered with the existing treatment of L-DOPA plus a DDCI, in patients with PD and end-of-dose motor fluctuations.
Secondary: To investigate the safety and tolerability of the combined treatment (L-DOPA/DDCI plus BIA 9-1067, entacapone, or placebo).

Protection of trial subjects:

The trial was conducted in accordance with the International Conference on Harmonisation (ICH), Good Clinical Practices (GCP), Good Manufacturing Practice (GMP), the ethical principles of the Declaration of Helsinki and with applicable local regulations. This trial was conducted by qualified persons who respected the rights and welfare of the subjects and after the review and approval of the protocol by an EC. Adverse events were collected throughout the trial and subject was followed by 14 days after the completion of the study.

Background therapy:

L-DOPA/DDCI (Carbidopa, Benserazide). Frequency: 3 to 8 daily doses. From V2 to V4 of the DB period, the investigator can decrease the daily dose of L-DOPA and DDCI (keeping the number of daily intakes unchanged), according to subject response. If the investigator finds that the dose reduction was too large, it can be increased again up to the baseline dose level. The dosage of L-DOPA/DDCI must not be changed during the study from V4 through the end of the DB period.

Evidence for comparator:

-

| | |
|---|---------------|
| Actual start date of recruitment | 30 March 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------------------|
| Country: Number of subjects enrolled | Austria: 3 |
| Country: Number of subjects enrolled | Bulgaria: 50 |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 16 |
| Country: Number of subjects enrolled | Czech Republic: 51 |
| Country: Number of subjects enrolled | Germany: 35 |
| Country: Number of subjects enrolled | Spain: 37 |
| Country: Number of subjects enrolled | France: 15 |
| Country: Number of subjects enrolled | Croatia: 14 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Hungary: 10 |
| Country: Number of subjects enrolled | Italy: 14 |
| Country: Number of subjects enrolled | Lithuania: 15 |
| Country: Number of subjects enrolled | Latvia: 7 |
| Country: Number of subjects enrolled | Poland: 90 |
| Country: Number of subjects enrolled | Portugal: 22 |
| Country: Number of subjects enrolled | Romania: 53 |
| Country: Number of subjects enrolled | Russian Federation: 34 |
| Country: Number of subjects enrolled | Serbia: 36 |
| Country: Number of subjects enrolled | Slovakia: 19 |
| Country: Number of subjects enrolled | Ukraine: 79 |
| Worldwide total number of subjects | 600 |
| EEA total number of subjects | 435 |

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) | 309 |
| From 65 to 84 years | 291 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Planned Number of Study Centres: 130 study centres in approximately 20 countries (Austria, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, France, Germany, Hungary, Italy, Latvia, Lithuania, Montenegro, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain and Ukraine).

Pre-assignment

Screening details:

Subjects who met all the inclusion criteria and none of the exclusion criteria. 679 subjects were enrolled to the trial and 79 subjects were screening failures. 1 subject was randomised but not treated.

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 679 ^[1] |
| Number of subjects completed | 599 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------------|
| Reason: Number of subjects | Adverse event, non-fatal: 2 |
| Reason: Number of subjects | Adverse event, serious non-fatal: 2 |
| Reason: Number of subjects | Consent withdrawn by subject: 29 |
| Reason: Number of subjects | Physician decision: 3 |
| Reason: Number of subjects | Protocol deviation: 1 |
| Reason: Number of subjects | Ineligibility: 38 |
| Reason: Number of subjects | Subject's non compliance: 1 |
| Reason: Number of subjects | Sponsor's discretion: 2 |
| Reason: Number of subjects | Insufficient medication in Germany: 1 |
| Reason: Number of subjects | Randomised, but not treated: 1 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects reported to have started the pre-assignment period is the number of enrolled subjects; The worldwide number is number of treated subjects.

Period 1

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

Arms

| | |
|---|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Part I - Placebo |
| Arm description: | |
| All placebo capsules will contain, on average, 1 mg riboflavin to mimic urinary discoloration seen as a harmless side effect of entacapone. | |
| Arm type | Placebo |

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

Dosage and administration details:

During the DB period, subjects will take 1 capsule of IMP concomitantly with each daytime L DOPA/DDCI dose (3 to 8 daily doses). An additional IMP bedtime dose will be administered at least 1 hour after the last daily dose of LDOPA/DDCI.

For the daytime doses (concomitantly with each L-DOPA/DDCI dose), the IMP administration will be as follows:

- placebo.

For the bedtime dose (at least 1 hour after the last daily dose of L-DOPA/DDCI), the IMP administration will be as follows:

- placebo.

The IMP intake (placebo) must start on the day after the Visit 2.

| | |
|------------------|---------------------------|
| Arm title | Part I - Entacapone 200mg |
|------------------|---------------------------|

Arm description:

Active substance: Entacapone

Trade name: Comtan®

Strength: Tablets 200 mg

Manufacturer: Novartis Pharmaceuticals

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Entacapone |
| Investigational medicinal product code | |
| Other name | Comtan® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

During the DB period, subjects will take 1 capsule of IMP concomitantly with each daytime L DOPA/DDCI dose (3 to 8 daily doses). An additional IMP bedtime dose will be administered at least 1 hour after the last daily dose of LDOPA/DDCI.

For the daytime doses (concomitantly with each L-DOPA/DDCI dose), the IMP administration will be as follows:

- 200 mg entacapone.

For the bedtime dose (at least 1 hour after the last daily dose of L-DOPA/DDCI), the IMP administration will be as follows:

- placebo.

The IMP intake (entacapone) must start on the day after the Visit 2.

| | |
|------------------|----------------------|
| Arm title | Part I - OPC 5mg/day |
|------------------|----------------------|

Arm description:

Active substance: BIA 9-1067

Other name: OPC, Opicapone

Strength: 5 mg

Manufacturer: BIAL – Portela & C^a SA, S. Mamede do Coronado, Portugal

| | |
|--|----------------|
| Arm type | Experimental |
| Investigational medicinal product name | BIA 9-1067 |
| Investigational medicinal product code | |
| Other name | OPC, Opicapone |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

During the DB period, subjects will take 1 capsule of IMP concomitantly with each daytime L DOPA/DDCI dose (3 to 8 daily doses). An additional IMP bedtime dose will be administered at least 1 hour after the last daily dose of LDOPA/DDCI.

For the daytime doses (concomitantly with each L-DOPA/DDCI dose), the IMP administration will be as follows:

- placebo.

For the bedtime dose (at least 1 hour after the last daily dose of L-DOPA/DDCI), the IMP administration will be as follows:

- 5 mg.

The IMP intake (BIA 9-1067) must start on the day after the Visit 2.

| | |
|---|-----------------------|
| Arm title | Part I - OPC 25mg/day |
| Arm description: | |
| Active substance: BIA 9-1067 | |
| Other name: OPC, Opicapone | |
| Strength: 25 mg | |
| Manufacturer: BIAL – Portela & C ^a SA, S. Mamede do Coronado, Portugal | |
| Arm type | Experimental |
| Investigational medicinal product name | BIA 9-1067 |
| Investigational medicinal product code | |
| Other name | OPC, Opicapone |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

During the DB period, subjects will take 1 capsule of IMP concomitantly with each daytime L DOPA/DDCI dose (3 to 8 daily doses). An additional IMP bedtime dose will be administered at least 1 hour after the last daily dose of LDOPA/DDCI.

For the daytime doses (concomitantly with each L-DOPA/DDCI dose), the IMP administration will be as follows:

- placebo.

For the bedtime dose (at least 1 hour after the last daily dose of L-DOPA/DDCI), the IMP administration will be as follows:

- 25 mg.

The IMP intake (BIA 9-1067) must start on the day after the Visit 2.

| | |
|---|-----------------------|
| Arm title | Part I - OPC 50mg/day |
| Arm description: | |
| Active substance: BIA 9-1067 | |
| Other name: OPC, Opicapone | |
| Strength: 50 mg | |
| Manufacturer: BIAL – Portela & C ^a SA, S. Mamede do Coronado, Portugal | |
| Arm type | Experimental |
| Investigational medicinal product name | BIA 9-1067 |
| Investigational medicinal product code | |
| Other name | OPC, Opicapone |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

During the DB period, subjects will take 1 capsule of IMP concomitantly with each daytime L DOPA/DDCI dose (3 to 8 daily doses). An additional IMP bedtime dose will be administered at least 1 hour after the last daily dose of LDOPA/DDCI.

For the daytime doses (concomitantly with each L-DOPA/DDCI dose), the IMP administration will be as follows:

- placebo.

For the bedtime dose (at least 1 hour after the last daily dose of L-DOPA/DDCI), the IMP administration will be as follows:

- 50 mg.

The IMP intake (BIA 9-1067) must start on the day after the Visit 2.

| Number of subjects in period 1^[2] | Part I - Placebo | Part I - Entacapone 200mg | Part I - OPC 5mg/day |
|---|------------------|---------------------------|----------------------|
| Started | 121 | 122 | 122 |
| Completed | 110 | 107 | 110 |
| Not completed | 11 | 15 | 12 |
| Consent withdrawn by subject | 4 | 6 | 3 |
| Physician decision | - | - | 1 |
| Adverse event, non-fatal | 4 | 5 | 4 |
| Adverse event, serious non-fatal | 1 | 1 | 1 |
| Ineligibility | 1 | 2 | - |
| Lost to follow-up | - | - | 1 |
| Sponsor's discretion | - | - | 1 |
| Protocol deviation | 1 | - | - |
| Subject's non compliance | - | 1 | - |
| Lack of efficacy | - | - | 1 |

| Number of subjects in period 1^[2] | Part I - OPC 25mg/day | Part I - OPC 50mg/day |
|---|-----------------------|-----------------------|
| Started | 119 | 115 |
| Completed | 108 | 107 |
| Not completed | 11 | 8 |
| Consent withdrawn by subject | 3 | 3 |
| Physician decision | 1 | - |
| Adverse event, non-fatal | 6 | 5 |
| Adverse event, serious non-fatal | - | - |
| Ineligibility | - | - |
| Lost to follow-up | - | - |
| Sponsor's discretion | - | - |
| Protocol deviation | - | - |
| Subject's non compliance | 1 | - |
| Lack of efficacy | - | - |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline period does not include 1 subject who was randomised but not treated.

Period 2

| | |
|------------------------------|-------------------|
| Period 2 title | Open-label period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|---|----------------|
| Arm title | Part II - OPC |
| Arm description: | |
| Active substance: BIA 9-1067 | |
| Other name: OPC, Opicapone | |
| Strength: 5 / 25 / 50 mg | |
| Manufacturer: BIAL – Portela & C ^a SA, S. Mamede do Coronado, Portugal | |
| Arm type | Experimental |
| Investigational medicinal product name | BIA 9-1067 |
| Investigational medicinal product code | |
| Other name | OPC, Opicapone |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

During the OL period, all subjects will take BIA 9-1067. Subjects will begin treatment at a dose of 25 mg BIA 9-1067 once daily at bedtime for the first week (7 days), regardless of their prior treatment in the DB period. If the “wearing-off” is not sufficiently controlled, and tolerability allows, the BIA 9-1067 dose can be adjusted by titrating up to 50 mg. If unacceptable dopaminergic AEs appear, usually reflected in an increased intensity or incidence of dyskinesias, the L-DOPA/DDCI dose should be adjusted first and only then; if not sufficient, the BIA 9-1067 dose can be down titrated as follows: subjects on 50 mg BIA 9-1067 should be down titrated first to 25 mg and if needed to 5 mg afterwards; subjects on 25 mg BIA 9-1067 should be down titrated to 5 mg. Adjustments of doses must be always done titrating upwards or downwards based on individual response and tolerability. From V13 to V14, the dose of L-DOPA/DDCI and BIA 9-1067 should remain stable.

| Number of subjects in period 2^[3] | Part II - OPC |
|---|---------------|
| Started | 495 |
| Completed | 432 |
| Not completed | 63 |
| Adverse event, serious fatal | 7 |
| Consent withdrawn by subject | 23 |
| Physician decision | 1 |
| Adverse event, non-fatal | 7 |
| Subject stopped IMP intake bef scheduled EOS visit | 3 |
| Adverse event, serious non-fatal | 9 |
| Lost to follow-up | 1 |
| Sponsor's discretion | 2 |
| Subject moved to other place | 4 |
| Lack of efficacy | 1 |
| Subject's non compliance | 5 |

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 542 subjects completed double blind part and 47 of them did not start open label part.

Baseline characteristics

Reporting groups

| | |
|--|---------------------------|
| Reporting group title | Part I - Placebo |
| Reporting group description: All placebo capsules will contain, on average, 1 mg riboflavin to mimic urinary discoloration seen as a harmless side effect of entacapone. | |
| Reporting group title | Part I - Entacapone 200mg |
| Reporting group description: Active substance: Entacapone Trade name: Comtan® Strength: Tablets 200 mg Manufacturer: Novartis Pharmaceuticals | |
| Reporting group title | Part I - OPC 5mg/day |
| Reporting group description: Active substance: BIA 9-1067 Other name: OPC, Opicapone Strength: 5 mg Manufacturer: BIAL – Portela & C ^a SA, S. Mamede do Coronado, Portugal | |
| Reporting group title | Part I - OPC 25mg/day |
| Reporting group description: Active substance: BIA 9-1067 Other name: OPC, Opicapone Strength: 25 mg Manufacturer: BIAL – Portela & C ^a SA, S. Mamede do Coronado, Portugal | |
| Reporting group title | Part I - OPC 50mg/day |
| Reporting group description: Active substance: BIA 9-1067 Other name: OPC, Opicapone Strength: 50 mg Manufacturer: BIAL – Portela & C ^a SA, S. Mamede do Coronado, Portugal | |

| Reporting group values | Part I - Placebo | Part I - Entacapone 200mg | Part I - OPC 5mg/day |
|--|------------------|---------------------------|----------------------|
| Number of subjects | 121 | 122 | 122 |
| Age Categorical | | | |
| Age Categorical Characteristic | | | |
| Units: Subjects | | | |
| In Utero | 0 | 0 | 0 |
| Preterm newborn- gestational age < 37 wk | 0 | 0 | 0 |
| Newborns (0-27days) | 0 | 0 | 0 |
| Infants and toddlers (28days – 23months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 year) | 0 | 0 | 0 |
| From 18 - 64 years | 60 | 66 | 65 |
| From 65 – 84 years | 61 | 56 | 57 |
| Over 85 years | 0 | 0 | 0 |
| Age Continuous | | | |
| Age Continuous Characteristic | | | |
| Units: Years | | | |
| arithmetic mean | 64.3 | 63.7 | 63.6 |

| | | | |
|--------------------|--------|--------|-------|
| standard deviation | ± 9.25 | ± 8.78 | ± 9.3 |
|--------------------|--------|--------|-------|

| | | | |
|-----------------------------------|----|----|----|
| Gender Categorical | | | |
| Gender Categorical Characteristic | | | |
| Units: Subjects | | | |
| Female | 71 | 46 | 51 |
| Male | 50 | 76 | 71 |

| Reporting group values | Part I - OPC 25mg/day | Part I - OPC 50mg/day | Total |
|---|--------------------------|--------------------------|-------|
| Number of subjects | 119 | 115 | 599 |
| Age Categorical | | | |
| Age Categorical Characteristic | | | |
| Units: Subjects | | | |
| In Utero | 0 | 0 | 0 |
| Preterm newborn- gestational age < 37 wk | 0 | 0 | 0 |
| Newborns (0-27days) | 0 | 0 | 0 |
| Infants and toddlers (28days – 23months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 year) | 0 | 0 | 0 |
| From 18 - 64 years | 59 | 58 | 308 |
| From 65 – 84 years | 60 | 57 | 291 |
| Over 85 years | 0 | 0 | 0 |
| Age Continuous | | | |
| Age Continuous Characteristic | | | |
| Units: Years | | | |
| arithmetic mean | 64.4 | 63.5 | |
| standard deviation | ± 8.98 | ± 9.22 | - |
| Gender Categorical | | | |
| Gender Categorical Characteristic | | | |
| Units: Subjects | | | |
| Female | 52 | 46 | 266 |
| Male | 67 | 69 | 333 |

End points

End points reporting groups

| | |
|---|------------------------------------|
| Reporting group title | Part I - Placebo |
| Reporting group description: All placebo capsules will contain, on average, 1 mg riboflavin to mimic urinary discoloration seen as a harmless side effect of entacapone. | |
| Reporting group title | Part I - Entacapone 200mg |
| Reporting group description: Active substance: Entacapone Trade name: Comtan® Strength: Tablets 200 mg Manufacturer: Novartis Pharmaceuticals | |
| Reporting group title | Part I - OPC 5mg/day |
| Reporting group description: Active substance: BIA 9-1067 Other name: OPC, Opicapone Strength: 5 mg Manufacturer: BIAL – Portela & C ^a SA, S. Mamede do Coronado, Portugal | |
| Reporting group title | Part I - OPC 25mg/day |
| Reporting group description: Active substance: BIA 9-1067 Other name: OPC, Opicapone Strength: 25 mg Manufacturer: BIAL – Portela & C ^a SA, S. Mamede do Coronado, Portugal | |
| Reporting group title | Part I - OPC 50mg/day |
| Reporting group description: Active substance: BIA 9-1067 Other name: OPC, Opicapone Strength: 50 mg Manufacturer: BIAL – Portela & C ^a SA, S. Mamede do Coronado, Portugal | |
| Reporting group title | Part II - OPC |
| Reporting group description: Active substance: BIA 9-1067 Other name: OPC, Opicapone Strength: 5 / 25 / 50 mg Manufacturer: BIAL – Portela & C ^a SA, S. Mamede do Coronado, Portugal | |
| Subject analysis set title | Part I - Placebo x Safety set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects who received at least 1 dose of IMP. | |
| Subject analysis set title | Part I - Entacapone x Safety set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects who received at least 1 dose of IMP. | |
| Subject analysis set title | Part I - OPC 5mg/day x Safety set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects who received at least 1 dose of IMP. | |
| Subject analysis set title | Part I - OPC 25mg/day x Safety set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects who received at least 1 dose of IMP. | |
| Subject analysis set title | Part I - OPC 50mg/day x Safety set |

| | |
|---|---|
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects who received at least 1 dose of IMP. | |
| Subject analysis set title | Part II - OPC x Safety set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects entered OL phase who received at least 1 dose of IMP of the OL phase. | |
| Subject analysis set title | Part I - Placebo x Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects randomised, treated with at least 1 dose of IMP after randomisation and with at least 1 OFF-time efficacy assessment. | |
| Subject analysis set title | Part I - Entacapone x Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects randomised, treated with at least 1 dose of IMP after randomisation and with at least 1 OFF-time efficacy assessment. | |
| Subject analysis set title | Part I - OPC 5mg/day x Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects randomised, treated with at least 1 dose of IMP after randomisation and with at least 1 OFF-time efficacy assessment. | |
| Subject analysis set title | Part I - OPC 25mg/day x Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects randomised, treated with at least 1 dose of IMP after randomisation and with at least 1 OFF-time efficacy assessment. | |
| Subject analysis set title | Part I - OPC 50mg/day x Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects randomised, treated with at least 1 dose of IMP after randomisation and with at least 1 OFF-time efficacy assessment. | |
| Subject analysis set title | Part I - Placebo x Per protocol set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects of the FAS without any major protocol deviations. Subjects were included into the PP set if they fulfilled all of the following criteria: - Fulfilling all inclusion criteria. - Treated with IMP according to the randomisation plan. - No Intake of prohibited concomitant medication. - Sufficient compliance. - No L-DOPA dose higher than baseline during the study from V4 through the end of the DB period. | |
| Subject analysis set title | Part I - Entacapone x Per protocol set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects of the FAS without any major protocol deviations. Subjects were included into the PP set if they fulfilled all of the following criteria: - Fulfilling all inclusion criteria. - Treated with IMP according to the randomisation plan. - No Intake of prohibited concomitant medication. - Sufficient compliance. - No L-DOPA dose higher than baseline during the study from V4 through the end of the DB period. | |
| Subject analysis set title | Part I - OPC 5mg/day x Per protocol set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects of the FAS without any major protocol deviations. Subjects were included into the PP set if they fulfilled all of the following criteria: | |

- Fulfilling all inclusion criteria.
- Treated with IMP according to the randomisation plan.
- No Intake of prohibited concomitant medication.
- Sufficient compliance.
- No L-DOPA dose higher than baseline during the study from V4 through the end of the DB period.

| | |
|----------------------------|--|
| Subject analysis set title | Part I - OPC 25mg/day x Per protocol set |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All subjects of the FAS without any major protocol deviations. Subjects were included into the PP set if they fulfilled all of the following criteria:

- Fulfilling all inclusion criteria.
- Treated with IMP according to the randomisation plan.
- No Intake of prohibited concomitant medication.
- Sufficient compliance.
- No L-DOPA dose higher than baseline during the study from V4 through the end of the DB period.

| | |
|----------------------------|--|
| Subject analysis set title | Part I - OPC 50mg/day x Per protocol set |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All subjects of the FAS without any major protocol deviations. Subjects were included into the PP set if they fulfilled all of the following criteria:

- Fulfilling all inclusion criteria.
- Treated with IMP according to the randomisation plan.
- No Intake of prohibited concomitant medication.
- Sufficient compliance.
- No L-DOPA dose higher than baseline during the study from V4 through the end of the DB period.

| | |
|----------------------------|---|
| Subject analysis set title | Part II - DB PLC / OL OPC x Full analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All subjects in DB treated with Placebo entering OL phase who received at least 1 dose of IMP of the OL phase and with at least 1 OFF-time efficacy assessment during the OL phase.

| | |
|----------------------------|---|
| Subject analysis set title | Part II - DB ENT / OL OPC x Full analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All subjects in DB treated with Entacapone entering OL phase who received at least 1 dose of IMP of the OL phase and with at least 1 OFF-time efficacy assessment during the OL phase.

| | |
|----------------------------|---|
| Subject analysis set title | Part II - DB OPC 5 / OL OPC x Full analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All subjects in DB treated with OPC 5mg/day entering OL phase who received at least 1 dose of IMP of the OL phase and with at least 1 OFF-time efficacy assessment during the OL phase.

| | |
|----------------------------|--|
| Subject analysis set title | Part II - DB OPC 25 / OL OPC x Full analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All subjects in DB treated with OPC 25mg/day entering OL phase who received at least 1 dose of IMP of the OL phase and with at least 1 OFF-time efficacy assessment during the OL phase.

| | |
|----------------------------|--|
| Subject analysis set title | Part II - DB OPC 50 / OL OPC x Full analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All subjects in DB treated with OPC 50mg/day entering OL phase who received at least 1 dose of IMP of the OL phase and with at least 1 OFF-time efficacy assessment during the OL phase.

| | |
|----------------------------|--|
| Subject analysis set title | Part II - DB PLC / OL OPC x Per protocol set |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All subjects of the OL-FAS (treated with Placebo in DB) without any major protocol deviation. Subjects

will be included

into the OL-PP if they fulfil all of the following criteria:

- Treated with OL-IMP
- Sufficient compliance (as assessed during the Data Review Meeting).
- No change in L-DOPA and/or OPC between Visit 13 and Visit 14
- Not identified as a major protocol violator for other reasons during the Data Review Meeting.

| | |
|----------------------------|--|
| Subject analysis set title | Part II - DB ENT / OL OPC x Per protocol set |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All subjects of the OL-FAS (treated with Entacapone in DB) without any major protocol deviation.

Subjects will be included

into the OL-PP if they fulfil all of the following criteria:

- Treated with OL-IMP
- Sufficient compliance (as assessed during the Data Review Meeting).
- No change in L-DOPA and/or OPC between Visit 13 and Visit 14
- Not identified as a major protocol violator for other reasons during the Data Review Meeting.

| | |
|----------------------------|--|
| Subject analysis set title | Part II - DB OPC 5 / OL OPC x Per protocol set |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All subjects of the OL-FAS (treated with OPC 5mg/day in DB) without any major protocol deviation.

Subjects will be included

into the OL-PP if they fulfil all of the following criteria:

- Treated with OL-IMP
- Sufficient compliance (as assessed during the Data Review Meeting).
- No change in L-DOPA and/or OPC between Visit 13 and Visit 14
- Not identified as a major protocol violator for other reasons during the Data Review Meeting.

| | |
|----------------------------|---|
| Subject analysis set title | Part II - DB OPC 25 / OL OPC x Per protocol set |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All subjects of the OL-FAS (treated with OPC 25mg/day in DB) without any major protocol deviation.

Subjects will be included

into the OL-PP if they fulfil all of the following criteria:

- Treated with OL-IMP
- Sufficient compliance (as assessed during the Data Review Meeting).
- No change in L-DOPA and/or OPC between Visit 13 and Visit 14
- Not identified as a major protocol violator for other reasons during the Data Review Meeting.

| | |
|----------------------------|---|
| Subject analysis set title | Part II - DB OPC 50 / OL OPC x Per protocol set |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All subjects of the OL-FAS (treated with OPC 50mg/day in DB) without any major protocol deviation.

Subjects will be included

into the OL-PP if they fulfil all of the following criteria:

- Treated with OL-IMP
- Sufficient compliance (as assessed during the Data Review Meeting).
- No change in L-DOPA and/or OPC between Visit 13 and Visit 14
- Not identified as a major protocol violator for other reasons during the Data Review Meeting.

Primary: Change from baseline in absolute OFF-time at the end of DB

| | |
|-----------------|--|
| End point title | Change from baseline in absolute OFF-time at the end of DB |
|-----------------|--|

End point description:

The primary efficacy variable will be the change from baseline in absolute OFF-time at the end of the DB period, This results refers when administered with the existing treatment of L-DOPA plus a DDCI, in patients with PD and end-of-dose motor fluctuations.

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

End point timeframe:

From Baseline to End of DB period

| End point values | Part I - Placebo x Full analysis set | Part I - Entacapone x Full analysis set | Part I - OPC 5mg/day x Full analysis set | Part I - OPC 25mg/day x Full analysis set |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 120 | 120 | 119 | 116 |
| Units: Minutes | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 370.1 (± 106.72) | 387.6 (± 130.47) | 403.2 (± 128.1) | 411.2 (± 132.29) |
| Endpoint | 325.3 (± 166.17) | 294.1 (± 165.64) | 307.2 (± 153.88) | 316.6 (± 162.21) |
| Change from Baseline to Endpoint | -44.8 (± 160.76) | -93.5 (± 155.55) | -96 (± 149.09) | -94.5 (± 162.02) |

| End point values | Part I - OPC 50mg/day x Full analysis set | Part I - Placebo x Per protocol set | Part I - Entacapone x Per protocol set | Part I - OPC 5mg/day x Per protocol set |
|--------------------------------------|--|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 115 | 112 | 104 | 110 |
| Units: Minutes | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 372.2 (± 106.95) | 374 (± 105.45) | 394.7 (± 110.67) | 406.1 (± 118.9) |
| Endpoint | 265.4 (± 142.54) | 328.3 (± 163.48) | 304.4 (± 155.66) | 307.1 (± 155.36) |
| Change from Baseline to Endpoint | -106.8 (± 134.2) | -45.7 (± 162.86) | -90.3 (± 136) | -99 (± 146.51) |

| End point values | Part I - OPC 25mg/day x Per protocol set | Part I - OPC 50mg/day x Per protocol set | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 105 | 106 | | |
| Units: Minutes | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 413.6 (± 126.26) | 367 (± 106.2) | | |
| Endpoint | 312.2 (± 154.89) | 263.6 (± 140.77) | | |
| Change from Baseline to Endpoint | -101.4 (± 156.96) | -103.4 (± 131.28) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Superiority (Part I): OPC 5mg/day vs Placebo FAS |
| Statistical analysis description: The primary efficacy objective is to demonstrate superiority. Results are based on an ANCOVA model with Treatment and Region as Factors and Baseline OFF-time as Covariate. | |
| Comparison groups | Part I - OPC 5mg/day x Full analysis set v Part I - Placebo x Full analysis set |
| Number of subjects included in analysis | 239 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0279 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | -35.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -71.4 |
| upper limit | 0.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 18.3846 |

| | |
|--|---|
| Statistical analysis title | Superiority (Part I): OPC 5mg/day vs Placebo PPS |
| Statistical analysis description: The primary efficacy objective is to demonstrate superiority. Results are based on an ANCOVA model with Treatment and Region as Factors and Baseline OFF-time as Covariate. | |
| Comparison groups | Part I - OPC 5mg/day x Per protocol set v Part I - Placebo x Per protocol set |
| Number of subjects included in analysis | 222 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0257 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | -36.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -73.1 |
| upper limit | 0.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 18.6485 |

| | |
|--|---|
| Statistical analysis title | Superiority (Part I): OPC 25mg/day vs Placebo FAS |
| Statistical analysis description: The primary efficacy objective is to demonstrate superiority. Results are based on an ANCOVA model with Treatment and Region as Factors and Baseline OFF-time as Covariate. | |

| | |
|---|--|
| Comparison groups | Part I - OPC 25mg/day x Full analysis set v Part I - Placebo x Full analysis set |
| Number of subjects included in analysis | 236 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0536 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | -29.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -66.3 |
| upper limit | 6.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 18.5437 |

| | |
|---|--|
| Statistical analysis title | Superiority (Part I): OPC 25mg/day vs Placebo PPS |
| Statistical analysis description: | |
| The primary efficacy objective is to demonstrate superiority. Results are based on an ANCOVA model with Treatment and Region as Factors and Baseline OFF-time as Covariate. | |
| Comparison groups | Part I - OPC 25mg/day x Per protocol set v Part I - Placebo x Per protocol set |
| Number of subjects included in analysis | 217 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0236 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | -37.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -74.7 |
| upper limit | -0.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 18.8924 |

| | |
|---|--|
| Statistical analysis title | Superiority (Part I): OPC 50mg/day vs Placebo FAS |
| Statistical analysis description: | |
| The primary efficacy objective is to demonstrate superiority. Results are based on an ANCOVA model with Treatment and Region as Factors and Baseline OFF-time as Covariate. | |
| Comparison groups | Part I - OPC 50mg/day x Full analysis set v Part I - Placebo x Full analysis set |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 235 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0005 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | -60.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -97.2 |
| upper limit | -24.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 18.5198 |

| | |
|---|--|
| Statistical analysis title | Superiority (Part I): OPC 50mg/day vs Placebo PPS |
| Statistical analysis description: | |
| The primary efficacy objective is to demonstrate superiority. Results are based on an ANCOVA model with Treatment and Region as Factors and Baseline OFF-time as Covariate. | |
| Comparison groups | Part I - OPC 50mg/day x Per protocol set v Part I - Placebo x Per protocol set |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0008 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | -59.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -96.3 |
| upper limit | -22.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 18.7827 |

| | |
|---|--|
| Statistical analysis title | Non-inferiority: OPC 5 mg/day vs Entacapone FAS |
| Statistical analysis description: | |
| The primary efficacy objective is to demonstrate non-inferiority. Results are based on an ANCOVA model with Treatment and Region as Factors and Baseline OFF-time as Covariate. | |
| Comparison groups | Part I - OPC 5mg/day x Full analysis set v Part I - Entacapone x Full analysis set |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 239 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.0867 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | 5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -31 |
| upper limit | 41 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 18.3243 |

| | |
|---|--|
| Statistical analysis title | Non-inferiority: OPC 5 mg/day vs Entacapone PPS |
| Statistical analysis description: | |
| The primary efficacy objective is to demonstrate non-inferiority. Results are based on an ANCOVA model with Treatment and Region as Factors and Baseline OFF-time as Covariate. | |
| Comparison groups | Part I - OPC 5mg/day x Per protocol set v Part I - Entacapone x Per protocol set |
| Number of subjects included in analysis | 214 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.0398 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | -3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -40.4 |
| upper limit | 33.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 18.9231 |

| | |
|---|---|
| Statistical analysis title | Non-inferiority: OPC 25 mg/day vs Entacapone FAS |
| Statistical analysis description: | |
| The primary efficacy objective is to demonstrate non-inferiority. Results are based on an ANCOVA model with Treatment and Region as Factors and Baseline OFF-time as Covariate. | |
| Comparison groups | Part I - OPC 25mg/day x Full analysis set v Part I - Entacapone x Full analysis set |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 236 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.1436 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | 10.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.9 |
| upper limit | 46.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 18.4617 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Non-inferiority: OPC 25 mg/day vs Entacapone PPS |
|-----------------------------------|--|

Statistical analysis description:

The primary efficacy objective is to demonstrate non-inferiority. Results are based on an ANCOVA model with Treatment and Region as Factors and Baseline OFF-time as Covariate.

| | |
|---|---|
| Comparison groups | Part I - OPC 25mg/day x Per protocol set v Part I - Entacapone x Per protocol set |
| Number of subjects included in analysis | 209 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.0366 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | -4.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -42 |
| upper limit | 33.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 19.148 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Non-inferiority: OPC 50 mg/day vs Entacapone FAS |
|-----------------------------------|--|

Statistical analysis description:

The primary efficacy objective is to demonstrate non-inferiority. Results are based on an ANCOVA model with Treatment and Region as Factors and Baseline OFF-time as Covariate.

| | |
|-------------------|---|
| Comparison groups | Part I - OPC 50mg/day x Full analysis set v Part I - Entacapone x Full analysis set |
|-------------------|---|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 235 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.0033 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | -20.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -56.9 |
| upper limit | 15.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 18.5075 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Non-inferiority: OPC 50 mg/day vs Entacapone PPS |
|-----------------------------------|--|

Statistical analysis description:

The primary efficacy objective is to demonstrate non-inferiority. Results are based on an ANCOVA with Treatment and Region as Factors and Baseline OFF-time as Covariate.

| | |
|---|---|
| Comparison groups | Part I - OPC 50mg/day x Per protocol set v Part I - Entacapone x Per protocol set |
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.0017 |
| Method | ANCOVA |
| Parameter estimate | Difference of LS Means |
| Point estimate | -26.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -63.8 |
| upper limit | 11.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 19.1323 |

Secondary: Total UPDRS SCORE (I, II (ON), and III)

| | |
|-----------------|---|
| End point title | Total UPDRS SCORE (I, II (ON), and III) |
|-----------------|---|

End point description:

Total UPDRS (Part I, II (ON) and III)

- UPDRS I evaluation of mentation, behavior, and mood
- UPDRS II self-evaluation of the activities of daily life (ADLs) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food
- UPDRS III clinician-scored monitored motor evaluation The UPDRS I, II and III scores and subscores are calculated as the sum of all individual items. If one or two items in a scale are missing, they will be imputed with the mean of the non-missing items of that scale.

Subscale has 0-4 ratings, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe
The final cumulative score will range from 0 (no disability) to 199 (total disability).

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

End point timeframe:

From Baseline to End of DB period

| End point values | Part I - Placebo x Full analysis set | Part I - Entacapone x Full analysis set | Part I - OPC 5mg/day x Full analysis set | Part I - OPC 25mg/day x Full analysis set |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 120 | 120 | 119 | 116 |
| Units: UPDRS Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 37.6 (± 16.56) | 35.4 (± 19.98) | 38.2 (± 16.16) | 40.1 (± 18.56) |
| Endpoint | 32.1 (± 14.87) | 29.8 (± 18.69) | 31 (± 15.98) | 32 (± 15.61) |
| Change from Baseline to Endpoint | -5.6 (± 10.3) | -6 (± 11.69) | -7.6 (± 9.96) | -7.6 (± 9.76) |

| End point values | Part I - OPC 50mg/day x Full analysis set | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 115 | | | |
| Units: UPDRS Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 38.8 (± 18.99) | | | |
| Endpoint | 31.5 (± 18.72) | | | |
| Change from Baseline to Endpoint | -6.5 (± 10.14) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Parkinson's Disease Sleep Scale (PDSS)

| | |
|-----------------|--|
| End point title | Parkinson's Disease Sleep Scale (PDSS) |
|-----------------|--|

End point description:

The Parkinson's disease Sleep Scale (PDSS) is a specific scale for the assessment of sleep disturbances in subjects with PD. The PDSS score is calculated as the sum of all single items. If one or two items are missing, they will be imputed with the mean of the non-missing items. If three or more items are missing, no imputation will be done and the score will be set to missing.

Subscale has 0-10 ratings, where 0 = severe and 10 = normal

The PDSS total score is a sum score of all 15 questions and ranges from 0 to 150, with lower scores meaning more disability.

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

End point timeframe:

From Baseline to End of DB period

| End point values | Part I - Placebo x Full analysis set | Part I - Entacapone x Full analysis set | Part I - OPC 5mg/day x Full analysis set | Part I - OPC 25mg/day x Full analysis set |
|--------------------------------------|--------------------------------------|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 120 | 120 | 119 | 116 |
| Units: PDS Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 97.5 (± 24.97) | 100.7 (± 25.46) | 97.8 (± 22.55) | 92.7 (± 26.85) |
| Endpoint | 98.5 (± 25.81) | 102.8 (± 24.98) | 102.9 (± 22.61) | 100.4 (± 23.75) |
| Change from Baseline to Endpoint | 1.3 (± 18.27) | 2 (± 20.64) | 5.4 (± 20.58) | 7.3 (± 22.11) |

| End point values | Part I - OPC 50mg/day x Full analysis set | | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 115 | | | |
| Units: PDS Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 98 (± 22.19) | | | |
| Endpoint | 100.9 (± 24.05) | | | |
| Change from Baseline to Endpoint | 3.1 (± 19.84) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Non-motor Symptoms Scale (NMSS)

| | |
|--|---------------------------------|
| End point title | Non-motor Symptoms Scale (NMSS) |
| End point description: | |
| <p>The Non-motor Symptoms Scale (NMSS) consists of 30 questions, covering 9 dimensions, whereby each item is scored for severity and frequency: Severity None 0 Mild (symptoms present but causes little distress) 1 Moderate (some distress or disturbance to subject) 2 Severe (major source of distress or disturbance to subject) 3</p> <p>Frequency Rarely (<1/wk) 1 Often (1/wk) 2 Frequent (several times per week) 3 Very Frequent (daily or all the time) 4</p> <p>The product of frequency and severity is calculated for each item and each dimension score is defined as the sum of the frequency*severity of the respective items. If frequency or severity of a single item is missing, the domain score will not be calculated. The NMSS total score is defined as the sum of all domain scores.</p> <p>The NMSS total score is calculated by adding all domain scores (0–360), and lower scores mean less disability.</p> | |
| End point type | Secondary |

End point timeframe:
From Baseline to End of DB period

| End point values | Part I - Placebo x Full analysis set | Part I - Entacapone x Full analysis set | Part I - OPC 5mg/day x Full analysis set | Part I - OPC 25mg/day x Full analysis set |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 118 ^[1] | 119 ^[2] | 117 ^[3] | 115 ^[4] |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 38.8 (± 29.2) | 32.1 (± 25.09) | 36.1 (± 26.67) | 39.8 (± 30.18) |
| Endpoint | 32 (± 25.71) | 27.5 (± 21.82) | 29.5 (± 24.3) | 34.4 (± 25.32) |
| Change from Baseline to Endpoint | -7 (± 15.09) | -4.2 (± 16.52) | -6.2 (± 13.24) | -5.7 (± 20.55) |

Notes:

- [1] - Two subjects did not complete questionnaire for baseline visit.
[2] - One subject did not complete questionnaire for baseline visit.
[3] - Two subjects did not complete questionnaire for baseline visit.
[4] - One subject did not complete questionnaire for baseline visit.

| End point values | Part I - OPC 50mg/day x Full analysis set | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 114 ^[5] | | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 36.4 (± 28.02) | | | |
| Endpoint | 33.4 (± 30.23) | | | |
| Change from Baseline to Endpoint | -2.8 (± 17.82) | | | |

Notes:

- [5] - One subject did not complete questionnaire for baseline visit.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Absolute OFF-time (minutes) during OL Phase – Change from OL Baseline

| | |
|-----------------|---|
| End point title | Absolute OFF-time (minutes) during OL Phase – Change from OL Baseline |
|-----------------|---|

End point description:

MMRM with Region as factor and baseline OFF-time as covariate will be used to assess the change of time course of OFF-time from OL Baseline to End of OL period

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From Baseline to End (Visit 14) of OL period

| End point values | Part II - DB PLC / OL OPC x Full analysis set | Part II - DB ENT / OL OPC x Full analysis set | Part II - DB OPC 5 / OL OPC x Full analysis set | Part II - DB OPC 25 / OL OPC x Full analysis set |
|-------------------------------------|--|--|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 98 | 100 | 100 | 98 |
| Units: Minutes | | | | |
| least squares mean (standard error) | | | | |
| Minutes | -64.9 (± 14.7653) | -39.3 (± 14.3752) | -27.5 (± 14.341) | -23 (± 14.3717) |

| End point values | Part II - DB OPC 50 / OL OPC x Full analysis set | Part II - DB PLC / OL OPC x Per protocol set | Part II - DB ENT / OL OPC x Per protocol set | Part II - DB OPC 5 / OL OPC x Per protocol set |
|-------------------------------------|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 98 | 93 | 93 | 94 |
| Units: Minutes | | | | |
| least squares mean (standard error) | | | | |
| Minutes | -1.8 (± 14.613) | -68 (± 14.6679) | -36.6 (± 14.4095) | -33.8 (± 14.4109) |

| End point values | Part II - DB OPC 25 / OL OPC x Per protocol set | Part II - DB OPC 50 / OL OPC x Per protocol set | | |
|-------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 95 | 90 | | |
| Units: Minutes | | | | |
| least squares mean (standard error) | | | | |
| Minutes | -24.1 (± 14.2067) | -5.6 (± 14.7093) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Part II: OPC 5mg/day vs Placebo FAS |
| Statistical analysis description: Results are based on MMRM with Region as factor and baseline OFF-time as covariate. | |
| Comparison groups | Part II - DB OPC 5 / OL OPC x Full analysis set v Part II - DB PLC / OL OPC x Full analysis set |

| | |
|---|---------------|
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0688 |
| Method | MMRM |

| | |
|--|---|
| Statistical analysis title | Part II: OPC 5mg/day vs Placebo PPS |
| Statistical analysis description: Results are based on MMRM with Region as factor and baseline OFF-time as covariate. | |
| Comparison groups | Part II - DB OPC 5 / OL OPC x Per protocol set v Part II - DB PLC / OL OPC x Per protocol set |
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0948 |
| Method | MMRM |

| | |
|--|---|
| Statistical analysis title | Part II: OPC 5mg/day vs Entacapone FAS |
| Statistical analysis description: Results are based on MMRM with Region as factor and baseline OFF-time as covariate. | |
| Comparison groups | Part II - DB OPC 5 / OL OPC x Full analysis set v Part II - DB ENT / OL OPC x Full analysis set |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.5602 |
| Method | MMRM |

| | |
|--|---|
| Statistical analysis title | Part II: OPC 5mg/day vs Entacapone PPS |
| Statistical analysis description: Results are based on MMRM with Region as factor and baseline OFF-time as covariate. | |
| Comparison groups | Part II - DB OPC 5 / OL OPC x Per protocol set v Part II - DB ENT / OL OPC x Per protocol set |
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.8912 |
| Method | MMRM |

| | |
|--|--------------------------------------|
| Statistical analysis title | Part II: OPC 25mg/day vs Placebo FAS |
| Statistical analysis description: Results are based on MMRM with Region as factor and baseline OFF-time as covariate. | |

| | |
|---|--|
| Comparison groups | Part II - DB OPC 25 / OL OPC x Full analysis set v Part II - DB PLC / OL OPC x Full analysis set |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0419 |
| Method | MMRM |

| | |
|---|--|
| Statistical analysis title | Part II: OPC 25mg/day vs Placebo PPS |
| Statistical analysis description: | |
| Results are based on MMRM with Region as factor and baseline OFF-time as covariate. | |
| Comparison groups | Part II - DB OPC 25 / OL OPC x Per protocol set v Part II - DB PLC / OL OPC x Per protocol set |
| Number of subjects included in analysis | 188 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.031 |
| Method | MMRM |

| | |
|---|--|
| Statistical analysis title | Part II: OPC 50mg/day vs Placebo FAS |
| Statistical analysis description: | |
| Results are based on MMRM with Region as factor and baseline OFF-time as covariate. | |
| Comparison groups | Part II - DB OPC 50 / OL OPC x Full analysis set v Part II - DB PLC / OL OPC x Full analysis set |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0024 |
| Method | MMRM |

| | |
|---|--|
| Statistical analysis title | Part II: OPC 50mg/day vs Placebo PPS |
| Statistical analysis description: | |
| Results are based on MMRM with Region as factor and baseline OFF-time as covariate. | |
| Comparison groups | Part II - DB OPC 50 / OL OPC x Per protocol set v Part II - DB PLC / OL OPC x Per protocol set |
| Number of subjects included in analysis | 183 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0026 |
| Method | MMRM |

| | |
|-----------------------------------|---|
| Statistical analysis title | Part II: OPC 25mg/day vs Entacapone FAS |
|-----------------------------------|---|

Statistical analysis description:

Results are based on MMRM with Region as factor and baseline OFF-time as covariate.

| | |
|---|--|
| Comparison groups | Part II - DB OPC 25 / OL OPC x Full analysis set v Part II - DB ENT / OL OPC x Full analysis set |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.4216 |
| Method | MMRM |

Statistical analysis title

Part II: OPC 25mg/day vs Entacapone PPS

Statistical analysis description:

Results are based on MMRM with Region as factor and baseline OFF-time as covariate.

| | |
|---|--|
| Comparison groups | Part II - DB OPC 25 / OL OPC x Per protocol set v Part II - DB ENT / OL OPC x Per protocol set |
| Number of subjects included in analysis | 188 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.5346 |
| Method | MMRM |

Statistical analysis title

Part II: OPC 50mg/day vs Entacapone FAS

Statistical analysis description:

Results are based on MMRM with Region as factor and baseline OFF-time as covariate.

| | |
|---|--|
| Comparison groups | Part II - DB OPC 50 / OL OPC x Full analysis set v Part II - DB ENT / OL OPC x Full analysis set |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.067 |
| Method | MMRM |

Statistical analysis title

Part II: OPC 50mg/day vs Entacapone PPS

Statistical analysis description:

Results are based on MMRM with Region as factor and baseline OFF-time as covariate.

| | |
|---|--|
| Comparison groups | Part II - DB OPC 50 / OL OPC x Per protocol set v Part II - DB ENT / OL OPC x Per protocol set |
| Number of subjects included in analysis | 183 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.1313 |
| Method | MMRM |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first intake of IMP until 2 weeks (14 days) after last intake of IMP in the corresponding part.

Adverse event reporting additional description:

The investigator monitor AEs and SAEs, at each visit, from V1 on throughout the study, using an unstructured interview. The investigator will inquire generally about the subject's well-being since the last visit. Details of any reported AEs were recorded at all scheduled and unscheduled visits as well as those reported during any telephone contact.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 14.0 |

Reporting groups

| | |
|--------------------------------|------------------------------------|
| Reporting group title | Part I - Placebo x Safety set |
| Reporting group description: - | |
| Reporting group title | Part I - OPC 5mg/day x Safety set |
| Reporting group description: - | |
| Reporting group title | Part I - Entacapone x Safety set |
| Reporting group description: - | |
| Reporting group title | Part I - OPC 25mg/day x Safety set |
| Reporting group description: - | |
| Reporting group title | Part II - OPC x Safety set |
| Reporting group description: - | |
| Reporting group title | Part I - OPC 50mg/day x Safety set |
| Reporting group description: - | |

| Serious adverse events | Part I - Placebo x Safety set | Part I - OPC 5mg/day x Safety set | Part I - Entacapone x Safety set |
|---|-------------------------------|-----------------------------------|----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 121 (4.96%) | 4 / 122 (3.28%) | 8 / 122 (6.56%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adrenal adenoma | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign ear neoplasm | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bowen's disease | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain neoplasm | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to spine | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small cell lung cancer stage unspecified | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superficial spreading melanoma stage unspecified | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Drug effect decreased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrothorax | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Aggression | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anxiety disorder due to a general medical condition | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jealous delusion | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Cardiac enzymes increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Hepatic enzyme increased subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Occult blood positive subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Contusion subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dislocation of vertebra subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Near drowning | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac asthma | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cor pulmonale acute | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cauda equina syndrome | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dementia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyskinesia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiculitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Gastritis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis acute | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stress urinary incontinence | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract inflammation | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Part I - OPC 25mg/day x Safety set | Part II - OPC x Safety set | Part I - OPC 50mg/day x Safety set |
|--|--|-------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 48 / 495 (9.70%) | 4 / 115 (3.48%) |
| number of deaths (all causes) | 0 | 11 | 0 |
| number of deaths resulting from adverse events | 0 | | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adrenal adenoma | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign ear neoplasm | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bowen's disease | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain neoplasm | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to spine | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small cell lung cancer stage unspecified | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Superficial spreading melanoma stage unspecified | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Hypertension | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Drug effect decreased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Sudden death | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrothorax | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Psychiatric disorders | | | |
| Aggression | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anxiety disorder due to a general medical condition | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jealous delusion | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Cardiac enzymes increased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Occult blood positive | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dislocation of vertebra | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Near drowning | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac asthma | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cor pulmonale acute | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Nervous system disorders | | | |
| Cauda equina syndrome | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dementia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyskinesia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiculitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency anaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis acute | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice cholestatic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stress urinary incontinence | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract inflammation | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Part I - Placebo x Safety set | Part I - OPC 5mg/day x Safety set | Part I - Entacapone x Safety set |
|--|--|--|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 59 / 121 (48.76%) | 62 / 122 (50.82%) | 67 / 122 (54.92%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Benign bone neoplasm | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fibrous histiocytoma | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemangioma | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lipoma | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Melanocytic naevus | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Prostatic adenoma | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Arteriosclerosis | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 4 / 122 (3.28%) | 2 / 122 (1.64%) |
| occurrences (all) | 2 | 4 | 2 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 2 / 122 (1.64%) | 3 / 122 (2.46%) |
| occurrences (all) | 0 | 2 | 3 |
| Orthostatic hypertension | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 2 / 122 (1.64%) |
| occurrences (all) | 0 | 0 | 2 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 2 / 122 (1.64%) |
| occurrences (all) | 0 | 0 | 2 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Post thrombotic syndrome | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Varicose vein | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vein disorder | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Venous insufficiency | | | |

| | | | |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Surgical and medical procedures | | | |
| Facial operation | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal septal operation | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ureteral meatotomy | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 3 / 122 (2.46%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 3 | 1 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Discomfort | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Drug effect decreased | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 1 / 122 (0.82%) | 3 / 122 (2.46%) |
| occurrences (all) | 3 | 2 | 3 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 3 / 122 (2.46%) | 3 / 122 (2.46%) |
| occurrences (all) | 2 | 3 | 3 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza like illness | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 121 (0.83%) 1 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Oedema subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 1 / 122 (0.82%) 1 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 2 / 122 (1.64%) 2 | 2 / 122 (1.64%) 3 |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 121 (0.83%) 1 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Sense of oppression subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Xerosis subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 1 / 122 (0.82%) 1 | 0 / 122 (0.00%) 0 |
| Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Social circumstances Gambling subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Social problem subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 1 / 122 (0.82%) 1 |
| Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Erectile dysfunction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Polycystic ovaries | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Prostatitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asphyxia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Asthma | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Choking | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 2 / 122 (1.64%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 1 | 1 |
| Oropharyngeal pain | | | |

| | | | |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Pulmonary oedema subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 1 / 122 (0.82%) 1 | 0 / 122 (0.00%) 0 |
| Psychiatric disorders | | | |
| Abnormal behaviour subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Abnormal dreams subjects affected / exposed occurrences (all) | 2 / 121 (1.65%) 2 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Agitation subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Anxiety subjects affected / exposed occurrences (all) | 4 / 121 (3.31%) 4 | 1 / 122 (0.82%) 1 | 2 / 122 (1.64%) 2 |
| Apathy subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Binge eating subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Bradyphrenia subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Compulsive shopping subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Confusional state subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Delirium subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |

| | | | |
|---------------------------------|-----------------|-----------------|-----------------|
| Delusion | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 1 / 122 (0.82%) |
| occurrences (all) | 1 | 1 | 1 |
| Depressive symptom | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Disorientation | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Distractibility | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Disturbance in sexual arousal | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dopamine dysregulation syndrome | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Emotional distress | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hallucination | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 1 / 122 (0.82%) |
| occurrences (all) | 1 | 3 | 1 |
| Hallucination, auditory | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hallucination, visual | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| Hallucinations, mixed | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypersexuality | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypochondriasis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Illogical thinking | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Illusion | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Impulse-control disorder | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Impulsive behaviour | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 2 / 122 (1.64%) | 7 / 122 (5.74%) |
| occurrences (all) | 1 | 2 | 8 |
| Jealous delusion | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Libido decreased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervousness | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nightmare | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Panic attack | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pathological gambling | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Persecutory delusion | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rapid eye movements sleep abnormal | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Restlessness | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sleep attacks | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Somnambulism | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alanine aminotransferase decreased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alanine aminotransferase increased | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Bilirubin conjugated increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood bilirubin unconjugated increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 2 / 122 (1.64%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 2 | 1 |
| Blood creatinine decreased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood glucose abnormal | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood lactate dehydrogenase increased | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood pressure decreased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood pressure systolic decreased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Body mass index increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram qt prolonged | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram repolarisation abnormality | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eosinophil count increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 2 | 0 | 1 |
| Glucose tolerance decreased | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Heart rate irregular | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Monocyte count increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 2 / 122 (1.64%) |
| occurrences (all) | 0 | 1 | 2 |
| Weight increased | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cell count decreased | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bone fissure | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest injury | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye penetration | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Face injury | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 2 / 122 (1.64%) | 3 / 122 (2.46%) |
| occurrences (all) | 3 | 3 | 4 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Head injury | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Laceration | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Post-traumatic pain | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin injury | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Suture related complication | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tooth injury | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-------------------------------------|-----------------|-----------------|-----------------|
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bundle branch block right | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 1 | 1 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 1 | 0 | 1 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|--------------------------------|-----------------|-----------------|-----------------|
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tricuspid valve incompetence | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Akinesia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 1 | 0 | 1 |
| Aphonia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bradykinesia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Burning sensation | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cauda equina syndrome | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chorea | | | |

| | | | |
|-----------------------------|-----------------|-------------------|------------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 2 / 122 (1.64%) | 5 / 122 (4.10%) |
| occurrences (all) | 1 | 2 | 5 |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyskinesia | | | |
| subjects affected / exposed | 5 / 121 (4.13%) | 17 / 122 (13.93%) | 10 / 122 (8.20%) |
| occurrences (all) | 5 | 17 | 12 |
| Dystonia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Formication | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Freezing phenomenon | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 2 / 122 (1.64%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Headache | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 1 / 122 (0.82%) | 3 / 122 (2.46%) |
| occurrences (all) | 3 | 1 | 4 |
| Hyperkinesia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypersomnia | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypokinesia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 1 / 122 (0.82%) |
| occurrences (all) | 1 | 2 | 1 |
| Hyporeflexia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypotonia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Intercostal neuralgia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mental impairment | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Motor dysfunction | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 2 | 0 | 1 |
| Movement disorder | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 2 / 122 (1.64%) |
| occurrences (all) | 0 | 0 | 2 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 1 / 122 (0.82%) | 1 / 122 (0.82%) |
| occurrences (all) | 2 | 1 | 1 |
| Parkinson's disease | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Parkinsonian gait | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Parkinsonian rest tremor | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Sudden onset of sleep | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Syncope | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Transient global amnesia subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Tremor subjects affected / exposed occurrences (all) | 2 / 121 (1.65%) 2 | 1 / 122 (0.82%) 1 | 2 / 122 (1.64%) 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 121 (0.83%) 1 | 1 / 122 (0.82%) 1 | 0 / 122 (0.00%) 0 |
| Anaemia megaloblastic subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Eosinophilia subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Leukocytosis subjects affected / exposed occurrences (all) | 1 / 121 (0.83%) 1 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| Ear congestion subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Ear haemorrhage subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Tinnitus | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vertigo | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Corneal disorder | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Diplopia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Glaucoma | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Periorbital oedema | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Pupils unequal | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|----------------------|----------------------|----------------------|
| Visual acuity reduced subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Visual impairment subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 1 / 122 (0.82%) 1 |
| Xerophthalmia subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 1 / 122 (0.82%) 1 |
| Gastrointestinal disorders | | | |
| Abdominal adhesions subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Abdominal distension subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 1 / 122 (0.82%) 1 | 0 / 122 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 1 / 122 (0.82%) 1 | 1 / 122 (0.82%) 1 |
| Cheilitis subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Colitis subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 3 / 121 (2.48%) 3 | 4 / 122 (3.28%) 5 | 5 / 122 (4.10%) 5 |
| Dental caries | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 122 (0.00%) | 3 / 122 (2.46%) |
| occurrences (all) | 2 | 0 | 3 |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 2 / 122 (1.64%) | 2 / 122 (1.64%) |
| occurrences (all) | 2 | 2 | 2 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 2 / 122 (1.64%) |
| occurrences (all) | 1 | 0 | 3 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Enamel anomaly | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epigastric discomfort | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis | | | |

| | | | |
|----------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gastritis atrophic | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal hypomotility | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperchlorhydria | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 121 (1.65%) | 2 / 122 (1.64%) | 8 / 122 (6.56%) |
| occurrences (all) | 2 | 2 | 14 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Tooth discolouration | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth disorder | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Biliary dyskinesia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Liver disorder | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|----------------------|----------------------|----------------------|
| Post cholecystectomy syndrome subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 1 / 122 (0.82%) 1 | 0 / 122 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis subjects affected / exposed occurrences (all) | 1 / 121 (0.83%) 1 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Alopecia subjects affected / exposed occurrences (all) | 1 / 121 (0.83%) 1 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Angioedema subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 1 / 122 (0.82%) 1 | 0 / 122 (0.00%) 0 |
| Dermal cyst subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Dermatitis subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 1 / 122 (0.82%) 1 |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 1 / 122 (0.82%) 1 |
| Eczema subjects affected / exposed occurrences (all) | 2 / 121 (1.65%) 2 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Erythema subjects affected / exposed occurrences (all) | 1 / 121 (0.83%) 1 | 0 / 122 (0.00%) 0 | 1 / 122 (0.82%) 1 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 4 / 121 (3.31%) 4 | 1 / 122 (0.82%) 1 | 1 / 122 (0.82%) 1 |
| Hyperkeratosis | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertrichosis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Intertrigo | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lentigo | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lichen planus | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Livedo reticularis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pigmentation disorder | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Precancerous skin lesion | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash papular | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seborrhoeic dermatitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin mass | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stasis dermatitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Telangiectasia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toxic skin eruption | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chromaturia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 3 / 122 (2.46%) |
| occurrences (all) | 0 | 0 | 3 |
| Dysuria | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| Enuresis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 2 / 122 (1.64%) |
| occurrences (all) | 0 | 0 | 2 |
| Incontinence | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ketonuria | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukocyturia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Micturition urgency | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Nocturia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oliguria | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Polyuria | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|----------------------|----------------------|----------------------|
| Renal colic subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Renal cyst subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Urge incontinence subjects affected / exposed occurrences (all) | 1 / 121 (0.83%) 1 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Urinary retention subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Endocrine disorders Hyperparathyroidism subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Ankle deformity subjects affected / exposed occurrences (all) | 1 / 121 (0.83%) 1 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Arthralgia subjects affected / exposed occurrences (all) | 2 / 121 (1.65%) 2 | 3 / 122 (2.46%) 3 | 1 / 122 (0.82%) 1 |
| Arthritis subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 5 / 121 (4.13%) 5 | 4 / 122 (3.28%) 4 | 1 / 122 (0.82%) 1 |
| Bursitis | | | |

| | | | |
|------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Camptocormia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Exostosis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Joint sprain | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Kyphosis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle rigidity | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 2 / 122 (1.64%) |
| occurrences (all) | 1 | 0 | 2 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 1 / 122 (0.82%) |
| occurrences (all) | 1 | 1 | 1 |
| Muscle tightness | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle twitching | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscular weakness | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 2 / 122 (1.64%) | 2 / 122 (1.64%) |
| occurrences (all) | 0 | 2 | 2 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 2 / 122 (1.64%) |
| occurrences (all) | 1 | 2 | 2 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 1 / 122 (0.82%) | 1 / 122 (0.82%) |
| occurrences (all) | 1 | 1 | 1 |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 2 / 122 (1.64%) | 2 / 122 (1.64%) |
| occurrences (all) | 2 | 3 | 2 |
| Osteochondrosis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Periarthritis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sensation of heaviness | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tendonitis | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 121 (0.00%) 0 | 0 / 122 (0.00%) 0 | 0 / 122 (0.00%) 0 |
| Infections and infestations | | | |
| Acute tonsillitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Bacteriuria | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Enterococcal infection | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal candidiasis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Helicobacter gastritis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------------|-----------------|-----------------|-----------------|
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 3 / 122 (2.46%) |
| occurrences (all) | 0 | 0 | 3 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 121 (4.13%) | 4 / 122 (3.28%) | 2 / 122 (1.64%) |
| occurrences (all) | 5 | 4 | 3 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Otitis externa | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Otitis media acute | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Sinusitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tinea pedis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tinea versicolour | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urethritis | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 2 / 122 (1.64%) | 2 / 122 (1.64%) |
| occurrences (all) | 0 | 2 | 2 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|------------------------------------|-----------------|-----------------|-----------------|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 1 / 122 (0.82%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 1 | 1 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyslipidaemia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 2 / 122 (1.64%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hyperphagia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Obesity | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 1 / 122 (0.82%) |
| occurrences (all) | 0 | 0 | 1 |
| Overweight | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitamin b12 deficiency | | | |
| subjects affected / exposed | 0 / 121 (0.00%) | 0 / 122 (0.00%) | 0 / 122 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Part I - OPC 25mg/day x Safety set | Part II - OPC x Safety set | Part I - OPC 50mg/day x Safety set |
|--|--|-------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 65 / 119 (54.62%) | 332 / 495 (67.07%) | 60 / 115 (52.17%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Benign bone neoplasm | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fibrous histiocytoma | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Haemangioma | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lipoma | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Melanocytic naevus | | | |

| | | | |
|-----------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed | 1 / 119 (0.84%) | 4 / 495 (0.81%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Prostatic adenoma | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 4 / 495 (0.81%) | 0 / 115 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematoma | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 12 / 495 (2.42%) | 2 / 115 (1.74%) |
| occurrences (all) | 2 | 12 | 2 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 6 / 495 (1.21%) | 0 / 115 (0.00%) |
| occurrences (all) | 2 | 6 | 0 |
| Orthostatic hypertension | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |

| | | | |
|--|----------------------|------------------------|----------------------|
| Orthostatic hypotension subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 16 / 495 (3.23%) 18 | 1 / 115 (0.87%) 1 |
| Phlebitis subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 1 / 115 (0.87%) 1 |
| Post thrombotic syndrome subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Varicose vein subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 2 / 495 (0.40%) 2 | 0 / 115 (0.00%) 0 |
| Vein disorder subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 0 / 115 (0.00%) 0 |
| Venous insufficiency subjects affected / exposed occurrences (all) | 1 / 119 (0.84%) 1 | 2 / 495 (0.40%) 2 | 0 / 115 (0.00%) 0 |
| Surgical and medical procedures | | | |
| Facial operation subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 1 / 115 (0.87%) 1 |
| Nasal septal operation subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 1 / 115 (0.87%) 1 |
| Ureteral meatotomy subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 1 / 115 (0.87%) 1 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 4 / 495 (0.81%) 4 | 0 / 115 (0.00%) 0 |
| Chest discomfort subjects affected / exposed occurrences (all) | 1 / 119 (0.84%) 1 | 0 / 495 (0.00%) 0 | 0 / 115 (0.00%) 0 |
| Chest pain | | | |

| | | | |
|-----------------------------|-----------------|-------------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Discomfort | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Drug effect decreased | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 59 / 495 (11.92%) | 2 / 115 (1.74%) |
| occurrences (all) | 1 | 67 | 2 |
| Fatigue | | | |
| subjects affected / exposed | 3 / 119 (2.52%) | 2 / 495 (0.40%) | 1 / 115 (0.87%) |
| occurrences (all) | 4 | 2 | 1 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 6 / 495 (1.21%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 2 / 495 (0.40%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 2 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sense of oppression | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Xerosis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|----------------------|----------------------|----------------------|
| Hypersensitivity subjects affected / exposed occurrences (all) | 1 / 119 (0.84%) 1 | 0 / 495 (0.00%) 0 | 1 / 115 (0.87%) 1 |
| Social circumstances Gambling subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Social problem subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 0 / 115 (0.00%) 0 |
| Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 2 / 495 (0.40%) 4 | 1 / 115 (0.87%) 1 |
| Erectile dysfunction subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Polycystic ovaries subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Prostatitis subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 0 / 115 (0.00%) 0 |
| Uterine polyp subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Asphyxia subjects affected / exposed occurrences (all) | 1 / 119 (0.84%) 1 | 0 / 495 (0.00%) 0 | 0 / 115 (0.00%) 0 |
| Asthma subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 0 / 115 (0.00%) 0 |
| Bronchospasm subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 0 / 115 (0.00%) 0 |

| | | | |
|-----------------------------|-----------------|------------------|-----------------|
| Choking | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 4 / 495 (0.81%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 1 | 1 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Abnormal behaviour | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abnormal dreams | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 4 / 495 (0.81%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Agitation | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 3 | 1 |
| Anxiety | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 11 / 495 (2.22%) | 2 / 115 (1.74%) |
| occurrences (all) | 2 | 12 | 2 |
| Apathy | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 2 / 115 (1.74%) |
| occurrences (all) | 0 | 0 | 2 |
| Binge eating | | | |

| | | | |
|---------------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed | 1 / 119 (0.84%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Bradyphrenia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Compulsive shopping | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Delirium | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Delusion | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 3 | 2 |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 1 | 1 |
| Depression | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 11 / 495 (2.22%) | 2 / 115 (1.74%) |
| occurrences (all) | 1 | 11 | 2 |
| Depressive symptom | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Disorientation | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Distractibility | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Disturbance in sexual arousal | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Dopamine dysregulation syndrome | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Emotional distress | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hallucination | | | |
| subjects affected / exposed | 6 / 119 (5.04%) | 8 / 495 (1.62%) | 1 / 115 (0.87%) |
| occurrences (all) | 6 | 9 | 1 |
| Hallucination, auditory | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 2 / 495 (0.40%) | 1 / 115 (0.87%) |
| occurrences (all) | 2 | 2 | 1 |
| Hallucination, visual | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 4 / 495 (0.81%) | 3 / 115 (2.61%) |
| occurrences (all) | 1 | 5 | 3 |
| Hallucinations, mixed | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypersexuality | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypochondriasis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Illogical thinking | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Illusion | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Impulse-control disorder | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Impulsive behaviour | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Insomnia | | | |

| | | | |
|------------------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed | 7 / 119 (5.88%) | 23 / 495 (4.65%) | 7 / 115 (6.09%) |
| occurrences (all) | 7 | 29 | 8 |
| Jealous delusion | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Libido decreased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervousness | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Nightmare | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 9 / 495 (1.82%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 10 | 0 |
| Panic attack | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 0 | 1 |
| Pathological gambling | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Persecutory delusion | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rapid eye movements sleep abnormal | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Restlessness | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sleep attacks | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 9 / 495 (1.82%) | 3 / 115 (2.61%) |
| occurrences (all) | 1 | 11 | 3 |

| | | | |
|---|-----------------|------------------|-----------------|
| Somnambulism | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Investigations | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Alanine aminotransferase decreased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 2 / 495 (0.40%) | 1 / 115 (0.87%) |
| occurrences (all) | 2 | 2 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 4 / 495 (0.81%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 5 | 1 |
| Bilirubin conjugated increased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood bilirubin unconjugated increased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 12 / 495 (2.42%) | 1 / 115 (0.87%) |
| occurrences (all) | 2 | 13 | 1 |

| | | | |
|--|----------------------|----------------------|----------------------|
| Blood creatinine decreased subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 2 / 495 (0.40%) 3 | 1 / 115 (0.87%) 1 |
| Blood glucose abnormal subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 0 / 115 (0.00%) 0 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 1 / 119 (0.84%) 1 | 4 / 495 (0.81%) 6 | 0 / 115 (0.00%) 0 |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Blood potassium increased subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 3 / 495 (0.61%) 3 | 0 / 115 (0.00%) 0 |
| Blood pressure decreased subjects affected / exposed occurrences (all) | 1 / 119 (0.84%) 1 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Blood pressure increased subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Blood pressure systolic decreased subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 0 / 115 (0.00%) 0 |
| Blood triglycerides increased subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 3 / 495 (0.61%) 4 | 0 / 115 (0.00%) 0 |
| Blood urea increased subjects affected / exposed occurrences (all) | 1 / 119 (0.84%) 1 | 2 / 495 (0.40%) 2 | 1 / 115 (0.87%) 1 |
| Body mass index increased | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electrocardiogram qt prolonged | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electrocardiogram repolarisation abnormality | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eosinophil count increased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 7 / 495 (1.41%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 8 | 0 |
| Glucose tolerance decreased | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Heart rate irregular | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Lymphocyte count decreased | | | |

| | | | |
|--|-----------------|------------------|-----------------|
| subjects affected / exposed | 2 / 119 (1.68%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Monocyte count increased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neutrophil count increased | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 12 / 495 (2.42%) | 4 / 115 (3.48%) |
| occurrences (all) | 0 | 12 | 5 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 2 | 1 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bone fissure | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chest injury | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Contusion | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Eye penetration | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Face injury | | | |

| | | | |
|-----------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fall | | | |
| subjects affected / exposed | 4 / 119 (3.36%) | 13 / 495 (2.63%) | 1 / 115 (0.87%) |
| occurrences (all) | 4 | 17 | 1 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Head injury | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Laceration | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Post-traumatic pain | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin injury | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Suture related complication | | | |

| | | | |
|-------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth injury | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 3 | 1 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 1 | 1 |
| Bundle branch block right | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 3 | 1 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--------------------------------|-----------------|-----------------|-----------------|
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 4 / 495 (0.81%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 2 | 1 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 3 / 495 (0.61%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 4 | 1 |
| Tricuspid valve incompetence | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 1 | 1 |
| Nervous system disorders | | | |
| Akinesia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aphonia | | | |

| | | | |
|-----------------------------|-----------------|-------------------|-------------------|
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bradykinesia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Burning sensation | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cauda equina syndrome | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Chorea | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 1 | 2 |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Disturbance in attention | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 2 | 0 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 6 / 119 (5.04%) | 8 / 495 (1.62%) | 3 / 115 (2.61%) |
| occurrences (all) | 7 | 10 | 3 |
| Dizziness postural | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 2 / 115 (1.74%) |
| occurrences (all) | 0 | 1 | 2 |
| Dyskinesia | | | |
| subjects affected / exposed | 9 / 119 (7.56%) | 72 / 495 (14.55%) | 18 / 115 (15.65%) |
| occurrences (all) | 13 | 88 | 19 |
| Dystonia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 9 / 495 (1.82%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 11 | 0 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Formication | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Freezing phenomenon | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 8 / 495 (1.62%) | 4 / 115 (3.48%) |
| occurrences (all) | 2 | 11 | 4 |
| Hyperkinesia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypersomnia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokinesia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 6 / 495 (1.21%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Hyporeflexia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypotonia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intercostal neuralgia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lumbar radiculopathy | | | |

| | | | |
|-----------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 2 / 115 (1.74%) |
| occurrences (all) | 0 | 3 | 2 |
| Mental impairment | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Motor dysfunction | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 4 / 495 (0.81%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Movement disorder | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Parkinson's disease | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 33 / 495 (6.67%) | 0 / 115 (0.00%) |
| occurrences (all) | 2 | 41 | 0 |
| Parkinsonian gait | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Parkinsonian rest tremor | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychomotor hyperactivity | | | |

| | | | |
|--------------------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 1 | 1 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 4 / 495 (0.81%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 4 / 119 (3.36%) | 7 / 495 (1.41%) | 2 / 115 (1.74%) |
| occurrences (all) | 4 | 7 | 2 |
| Sudden onset of sleep | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Transient global amnesia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tremor | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 16 / 495 (3.23%) | 1 / 115 (0.87%) |
| occurrences (all) | 2 | 19 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 8 / 495 (1.62%) | 1 / 115 (0.87%) |
| occurrences (all) | 2 | 8 | 1 |
| Anaemia megaloblastic | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eosinophilia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|----------------------|----------------------|----------------------|
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| Ear congestion subjects affected / exposed occurrences (all) | 1 / 119 (0.84%) 1 | 0 / 495 (0.00%) 0 | 1 / 115 (0.87%) 1 |
| Ear haemorrhage subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 1 / 115 (0.87%) 1 |
| Tinnitus subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Vertigo subjects affected / exposed occurrences (all) | 3 / 119 (2.52%) 3 | 2 / 495 (0.40%) 2 | 0 / 115 (0.00%) 0 |
| Eye disorders | | | |
| Cataract subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Corneal disorder subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 0 / 115 (0.00%) 0 |
| Diplopia subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 2 / 495 (0.40%) 2 | 0 / 115 (0.00%) 0 |
| Dry eye subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Glaucoma | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Periorbital oedema | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pupils unequal | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 1 | 1 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 1 | 1 |
| Xerophthalmia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal adhesions | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 2 / 495 (0.40%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 2 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 119 (2.52%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 5 | 3 | 0 |

| | | | |
|-----------------------------|-----------------|------------------|-----------------|
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 15 / 495 (3.03%) | 7 / 115 (6.09%) |
| occurrences (all) | 0 | 16 | 8 |
| Dental caries | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 4 / 495 (0.81%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 4 | 1 |
| Dry mouth | | | |
| subjects affected / exposed | 3 / 119 (2.52%) | 10 / 495 (2.02%) | 2 / 115 (1.74%) |
| occurrences (all) | 3 | 10 | 2 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 2 / 495 (0.40%) | 3 / 115 (2.61%) |
| occurrences (all) | 2 | 3 | 3 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Enamel anomaly | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|----------------------------------|-----------------|-----------------|-----------------|
| Enteritis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Epigastric discomfort | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Gastritis atrophic | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal hypomotility | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| Haematochezia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperchlorhydria | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 3 / 119 (2.52%) | 7 / 495 (1.41%) | 3 / 115 (2.61%) |
| occurrences (all) | 3 | 10 | 3 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 1 | 1 |
| Tooth discolouration | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tooth disorder | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 119 (2.52%) | 3 / 495 (0.61%) | 1 / 115 (0.87%) |
| occurrences (all) | 3 | 4 | 1 |
| Hepatobiliary disorders | | | |
| Biliary dyskinesia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cholecystitis | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Liver disorder | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Post cholecystectomy syndrome | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 2 | 1 | 1 |
| Alopecia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Angioedema | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermal cyst | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 1 | 1 |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 5 / 495 (1.01%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| Dry skin | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 1 | 1 |
| Eczema | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 5 / 495 (1.01%) | 0 / 115 (0.00%) |
| occurrences (all) | 3 | 5 | 0 |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypertrichosis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intertrigo | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 2 | 1 |
| Lentigo | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lichen planus | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Livedo reticularis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pigmentation disorder | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Precancerous skin lesion | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| Pruritus | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 2 / 115 (1.74%) |
| occurrences (all) | 1 | 1 | 2 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Seborrhoeic dermatitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin mass | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stasis dermatitis | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Telangiectasia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Toxic skin eruption | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| Urticaria | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chromaturia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Enuresis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 1 | 1 |
| Incontinence | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ketonuria | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Leukocyturia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Micturition urgency | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 2 | 1 |
| Nocturia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 119 (1.68%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Oliguria | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Polyuria | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal cyst | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Urge incontinence | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 5 / 495 (1.01%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Endocrine disorders | | | |
| Hyperparathyroidism | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|-----------------|------------------|-----------------|
| Musculoskeletal and connective tissue disorders | | | |
| Ankle deformity | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 7 / 495 (1.41%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 8 | 0 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 1 | 1 |
| Back pain | | | |
| subjects affected / exposed | 3 / 119 (2.52%) | 23 / 495 (4.65%) | 0 / 115 (0.00%) |
| occurrences (all) | 3 | 24 | 0 |
| Bursitis | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Camptocormia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Exostosis | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Joint sprain | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Kyphosis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle haemorrhage | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscle rigidity | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 5 / 495 (1.01%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 5 | 1 |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 119 (3.36%) | 2 / 495 (0.40%) | 1 / 115 (0.87%) |
| occurrences (all) | 4 | 2 | 2 |
| Muscle tightness | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 3 |
| Muscle twitching | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 4 / 495 (0.81%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Osteochondrosis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain in extremity | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 4 / 495 (0.81%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Periarthritis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Sensation of heaviness | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 5 / 495 (1.01%) | 0 / 115 (0.00%) |
| occurrences (all) | 2 | 5 | 0 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tendonitis | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Infections and infestations | | | |
| Acute tonsillitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bacteriuria | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Enterococcal infection | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fungal infection | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| | | | |
|-----------------------------------|-----------------|------------------|-----------------|
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 2 | 1 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal candidiasis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Helicobacter gastritis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 8 / 495 (1.62%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 8 | 1 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 16 / 495 (3.23%) | 1 / 115 (0.87%) |
| occurrences (all) | 2 | 18 | 1 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 4 / 495 (0.81%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |

| | | | |
|-----------------------------------|-----------------|-----------------|-----------------|
| Otitis externa | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Otitis media acute | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 4 | 1 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 9 / 495 (1.82%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 10 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tinea pedis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 2 / 495 (0.40%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Tinea versicolour | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 3 / 495 (0.61%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 3 | 1 |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|----------------------|------------------------|----------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 2 / 495 (0.40%) 2 | 0 / 115 (0.00%) 0 |
| Urethritis subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 0 / 495 (0.00%) 0 | 1 / 115 (0.87%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 119 (0.84%) 1 | 11 / 495 (2.22%) 12 | 1 / 115 (0.87%) 1 |
| Viral infection subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 5 / 495 (1.01%) 5 | 0 / 115 (0.00%) 0 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Diabetes mellitus subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 6 / 495 (1.21%) 6 | 0 / 115 (0.00%) 0 |
| Dyslipidaemia subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 2 / 495 (0.40%) 2 | 0 / 115 (0.00%) 0 |
| Glucose tolerance impaired subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Gout subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 3 | 0 / 115 (0.00%) 0 |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 0 / 119 (0.00%) 0 | 1 / 495 (0.20%) 1 | 0 / 115 (0.00%) 0 |
| Hyperglycaemia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Hyperphagia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 3 / 495 (0.61%) | 0 / 115 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 0 / 495 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all) | 0 | 0 | 1 |
| Obesity | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 5 / 495 (1.01%) | 1 / 115 (0.87%) |
| occurrences (all) | 1 | 5 | 1 |
| Overweight | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vitamin b12 deficiency | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 495 (0.20%) | 0 / 115 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 10 May 2011 | <p>Global Amendment #1</p> <p>The reason for this study global protocol amendment #1 is to implement administrative changes and to correct typing errors.</p> <p>The following modifications to the protocol were introduced by this amendment:</p> <p>The central 12-lead ECG reading and central diary evaluation will be implemented.</p> <p>The duration of ECG readings is changed to 10 seconds instead of 15 seconds.</p> <p>Randomisation number will be integrated in the eCRF.</p> <p>Start day of the IMP intake is indicated.</p> <p>Investigator's and subject's assessment of change will not be performed at Visit 2.</p> <p>Specific gravity of the urine will not be assessed by the dipstick.</p> <p>Unithink NV, subcontracted supplier for the e-CRF, diary and IRS was changed to Perceptive eClinical Limited.</p> <p>Parkinson's Disease Sleep Scale is corrected.</p> |
| 30 August 2011 | <p>Global Amendment #2</p> <p>This amendment to study protocol BIA-91067-301 has been prepared mainly to address comments from the US Food and Drug Administration (FDA). The study design has been changed for all sites as follows:</p> <ul style="list-style-type: none">• Additional vital signs and 12-lead electrocardiogram (ECG) measurements were added, and• Bicarbonate was added to the biochemistry laboratory test panel, and• The Modified Minnesota Impulsive Disorders Interview (mMIDI) and Columbia Suicide Severity Rating Scale (C-SSRS) were added to the assessment scales, and• Skin examinations by a dermatologist were added for screening for melanoma, and• Clarification on the adjustment of the BIA 9-1067 and levodopa (L-DOPA)/dopa decarboxylase inhibitor (DDCI) doses during the open-label period was added. <p>The FDA, after their review of the initial Investigational New Drug Application for BIA 9-1067, recommended collection of additional safety data.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported