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 & Cª 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 & Cª 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 & Cª 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 & Cª 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 & Cª 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 & Cª 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 & Cª 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 & Cª 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 & Cª 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 & Cª 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 & Cª 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:

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
Frequency Rarely (<1/wk) 1 Often (1/wk) 2 Frequent (several times per week) 3 Very Frequent (daily or all the time) 4
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.
The NMSS total score is calculated by adding all domain scores (0–360), and lower scores mean less 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	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	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	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	1 / 121 (0.83%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	1 / 122 (0.82%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 121 (0.00%)	2 / 122 (1.64%)	2 / 122 (1.64%)
occurrences (all)	0	2	3
Pyrexia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	1	0	0
Sense of oppression			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Xerosis			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 121 (0.00%)	1 / 122 (0.82%)	0 / 122 (0.00%)
occurrences (all)	0	1	0
Hypersensitivity			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Social circumstances			
Gambling			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Social problem			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	1 / 122 (0.82%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	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	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Pulmonary oedema			
subjects affected / exposed	0 / 121 (0.00%)	1 / 122 (0.82%)	0 / 122 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Abnormal dreams			
subjects affected / exposed	2 / 121 (1.65%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	2	0	0
Agitation			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	4 / 121 (3.31%)	1 / 122 (0.82%)	2 / 122 (1.64%)
occurrences (all)	4	1	2
Apathy			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Binge eating			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Bradyphrenia			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Compulsive shopping			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Delirium			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	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	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	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	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Transient global amnesia			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	2 / 121 (1.65%)	1 / 122 (0.82%)	2 / 122 (1.64%)
occurrences (all)	2	1	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 121 (0.83%)	1 / 122 (0.82%)	0 / 122 (0.00%)
occurrences (all)	1	1	0
Anaemia megaloblastic			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Eosinophilia			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Leukocytosis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	1	0	0
Leukopenia			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Ear haemorrhage			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	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	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	1 / 122 (0.82%)
occurrences (all)	0	0	1
Xerophthalmia			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	1 / 122 (0.82%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 121 (0.00%)	1 / 122 (0.82%)	0 / 122 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 121 (0.00%)	1 / 122 (0.82%)	1 / 122 (0.82%)
occurrences (all)	0	1	1
Cheilitis			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	3 / 121 (2.48%)	4 / 122 (3.28%)	5 / 122 (4.10%)
occurrences (all)	3	5	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	0 / 121 (0.00%)	1 / 122 (0.82%)	0 / 122 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	1	0	0
Angioedema			
subjects affected / exposed	0 / 121 (0.00%)	1 / 122 (0.82%)	0 / 122 (0.00%)
occurrences (all)	0	1	0
Dermal cyst			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	1 / 122 (0.82%)
occurrences (all)	0	0	1
Dermatitis allergic			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	1 / 122 (0.82%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	2 / 121 (1.65%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	2	0	0
Erythema			
subjects affected / exposed	1 / 121 (0.83%)	0 / 122 (0.00%)	1 / 122 (0.82%)
occurrences (all)	1	0	1
Hyperhidrosis			
subjects affected / exposed	4 / 121 (3.31%)	1 / 122 (0.82%)	1 / 122 (0.82%)
occurrences (all)	4	1	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	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Renal cyst			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Urge incontinence			
subjects affected / exposed	1 / 121 (0.83%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	1	0	0
Urinary incontinence			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Ankle deformity			
subjects affected / exposed	1 / 121 (0.83%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	2 / 121 (1.65%)	3 / 122 (2.46%)	1 / 122 (0.82%)
occurrences (all)	2	3	1
Arthritis			
subjects affected / exposed	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	5 / 121 (4.13%)	4 / 122 (3.28%)	1 / 122 (0.82%)
occurrences (all)	5	4	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	0 / 121 (0.00%)	0 / 122 (0.00%)	0 / 122 (0.00%)
occurrences (all)	0	0	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	0 / 119 (0.00%)	16 / 495 (3.23%)	1 / 115 (0.87%)
occurrences (all)	0	18	1
Phlebitis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	1 / 115 (0.87%)
occurrences (all)	0	0	1
Post thrombotic syndrome			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Varicose vein			
subjects affected / exposed	0 / 119 (0.00%)	2 / 495 (0.40%)	0 / 115 (0.00%)
occurrences (all)	0	2	0
Vein disorder			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	0 / 115 (0.00%)
occurrences (all)	0	0	0
Venous insufficiency			
subjects affected / exposed	1 / 119 (0.84%)	2 / 495 (0.40%)	0 / 115 (0.00%)
occurrences (all)	1	2	0
Surgical and medical procedures			
Facial operation			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	1 / 115 (0.87%)
occurrences (all)	0	0	1
Nasal septal operation			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	1 / 115 (0.87%)
occurrences (all)	0	0	1
Ureteral meatotomy			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	1 / 115 (0.87%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 119 (0.00%)	4 / 495 (0.81%)	0 / 115 (0.00%)
occurrences (all)	0	4	0
Chest discomfort			
subjects affected / exposed	1 / 119 (0.84%)	0 / 495 (0.00%)	0 / 115 (0.00%)
occurrences (all)	1	0	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	1 / 119 (0.84%)	0 / 495 (0.00%)	1 / 115 (0.87%)
occurrences (all)	1	0	1
Social circumstances			
Gambling			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Social problem			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	0 / 115 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 119 (0.00%)	2 / 495 (0.40%)	1 / 115 (0.87%)
occurrences (all)	0	4	1
Erectile dysfunction			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Polycystic ovaries			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Prostatitis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	0 / 115 (0.00%)
occurrences (all)	0	0	0
Uterine polyp			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 495 (0.00%)	0 / 115 (0.00%)
occurrences (all)	1	0	0
Asthma			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	0 / 115 (0.00%)
occurrences (all)	0	0	0
Bronchospasm			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	0 / 115 (0.00%)
occurrences (all)	0	0	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	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 119 (0.00%)	2 / 495 (0.40%)	1 / 115 (0.87%)
occurrences (all)	0	3	1
Blood glucose abnormal			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	0 / 115 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			
subjects affected / exposed	1 / 119 (0.84%)	4 / 495 (0.81%)	0 / 115 (0.00%)
occurrences (all)	1	6	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Blood potassium increased			
subjects affected / exposed	0 / 119 (0.00%)	3 / 495 (0.61%)	0 / 115 (0.00%)
occurrences (all)	0	3	0
Blood pressure decreased			
subjects affected / exposed	1 / 119 (0.84%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	1	1	0
Blood pressure increased			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Blood pressure systolic decreased			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	0 / 115 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 119 (0.00%)	3 / 495 (0.61%)	0 / 115 (0.00%)
occurrences (all)	0	4	0
Blood urea increased			
subjects affected / exposed	1 / 119 (0.84%)	2 / 495 (0.40%)	1 / 115 (0.87%)
occurrences (all)	1	2	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	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	1 / 119 (0.84%)	0 / 495 (0.00%)	1 / 115 (0.87%)
occurrences (all)	1	0	1
Ear haemorrhage			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	1 / 115 (0.87%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	3 / 119 (2.52%)	2 / 495 (0.40%)	0 / 115 (0.00%)
occurrences (all)	3	2	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Corneal disorder			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	0 / 115 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	0 / 119 (0.00%)	2 / 495 (0.40%)	0 / 115 (0.00%)
occurrences (all)	0	2	0
Dry eye			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	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	0 / 119 (0.00%)	2 / 495 (0.40%)	0 / 115 (0.00%)
occurrences (all)	0	2	0
Urethritis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 495 (0.00%)	1 / 115 (0.87%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	1 / 119 (0.84%)	11 / 495 (2.22%)	1 / 115 (0.87%)
occurrences (all)	1	12	1
Viral infection			
subjects affected / exposed	0 / 119 (0.00%)	5 / 495 (1.01%)	0 / 115 (0.00%)
occurrences (all)	0	5	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Diabetes mellitus			
subjects affected / exposed	0 / 119 (0.00%)	6 / 495 (1.21%)	0 / 115 (0.00%)
occurrences (all)	0	6	0
Dyslipidaemia			
subjects affected / exposed	0 / 119 (0.00%)	2 / 495 (0.40%)	0 / 115 (0.00%)
occurrences (all)	0	2	0
Glucose tolerance impaired			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Gout			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	3	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 495 (0.20%)	0 / 115 (0.00%)
occurrences (all)	0	1	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	Global Amendment #1 The reason for this study global protocol amendment #1 is to implement administrative changes and to correct typing errors. The following modifications to the protocol were introduced by this amendment: The central 12-lead ECG reading and central diary evaluation will be implemented. The duration of ECG readings is changed to 10 seconds instead of 15 seconds. Randomisation number will be integrated in the eCRF. Start day of the IMP intake is indicated. Investigator's and subject's assessment of change will not be performed at Visit 2. Specific gravity of the urine will not be assessed by the dipstick. Unithink NV, subcontracted supplier for the e-CRF, diary and IRS was changed to Perceptive eClinical Limited. Parkinson's Disease Sleep Scale is corrected.
30 August 2011	Global Amendment #2 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: • 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. The FDA, after their review of the initial Investigational New Drug Application for BIA 9-1067, recommended collection of additional safety data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported