

**Clinical trial results:  
Efficacy and safety of opicapone in clinical practice in Parkinson's  
Disease patients with wearing-off motor fluctuations****Summary**

EudraCT number	2016-002391-27
Trial protocol	GB DE
Global end of trial date	10 July 2019

**Results information**

Result version number	v1 (current)
This version publication date	17 October 2019
First version publication date	17 October 2019
Summary attachment (see zip file)	Synopsis (BIA-OPC-401-ITR-Synopsis-V1-0-10JUL2019.pdf)

**Trial information****Trial identification**

Sponsor protocol code	BIA-OPC-401
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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
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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	17 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 July 2018
Global end of trial reached?	Yes
Global end of trial date	10 July 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the change in subject's condition according to the Investigator's Global Assessment of Change after three months of treatment with 50 mg opicapone once daily in a heterogeneous patient population reflecting daily clinical practice.

Protection of trial subjects:

This trial will be performed in specialised neurological centres and neurological private practices. The trial will be conducted in compliance with this protocol, by trial personnel, who are qualified by education, training, and experience in their roles, with adherence to Good Clinical Practice (GCP), the applicable regulatory requirements, and ethical principles based on the Declaration of Helsinki.

Background therapy:

L-dopa/DDCI

Evidence for comparator: -

Actual start date of recruitment	23 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 372
Country: Number of subjects enrolled	United Kingdom: 134
Worldwide total number of subjects	506
EEA total number of subjects	506

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)	167

From 65 to 84 years	333
85 years and over	6

## Subject disposition

### Recruitment

Recruitment details:

Subjects of  $\geq 30$  years of age with documented history of diagnosed with idiopathic PD and treated with three to seven daily doses of L-dopa/DDCI or L-dopa/DDCI/entacapone were recruited.

### Pre-assignment

Screening details:

506 subjects were enrolled. 4 subjects were screening failures. Further 7 screened subjects prematurely discontinued from the trial before taking IMP.

### Pre-assignment period milestones

Number of subjects started	506
Number of subjects completed	495

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 4
Reason: Number of subjects	Ineligibility: 4
Reason: Number of subjects	Other: 2
Reason: Number of subjects	Non-compliance: 1

### Period 1

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

### Arms

Arm title	Opicapone
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Arm description:

Opicapone (BIA 9-1067), 50mg hard capsules, once daily in the evening

Arm type	Experimental
Investigational medicinal product name	Opicapone
Investigational medicinal product code	OPC
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

All subjects will start treatment with 50 mg OPC in the evening on the day of Visit 1 and will take 50 mg OPC once daily throughout the entire trial. The last OPC intake will take place in the evening prior to Visit 4.

The 50 mg OPC capsule has to be taken once daily at bedtime at least one hour before or after the last L-dopa/DDCI dose.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Opicapone
Started	495
Completed	386
Not completed	109
Consent withdrawn by subject	14
Adverse event, non-fatal	76
Other	4
Non-compliance	2
Adverse event, serious non-fatal	8
Development of exclusion criterion	2
Lack of efficacy	3

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Notes:

[1] - 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 a screening failure.

## Baseline characteristics

### Reporting groups

Reporting group title	Opicapone
Reporting group description:	
Opicapone (BIA 9-1067), 50mg hard capsules, once daily in the evening	

Reporting group values	Opicapone	Total	
Number of subjects	495	495	
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			
In Utero	0	0	
Preterm newborn- gestational age < 37 wk	0	0	
Newborns (0-27days)	0	0	
Infants and toddlers (28days - 23months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 year)	0	0	
From 18 - 64 years	164	164	
From 65 - 84 years	325	325	
Over 85 years	6	6	
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	67.7		
standard deviation	± 8.98	-	
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	179	179	
Male	315	315	
Missing	1	1	

## End points

### End points reporting groups

Reporting group title	Opicapone
Reporting group description:	Opicapone (BIA 9-1067), 50mg hard capsules, once daily in the evening
Subject analysis set title	Opicapone x Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	All subjects who received at least one dose of OPC.
Subject analysis set title	Opicapone x Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	All subjects treated with at least one dose of OPC and with at least one Investigator's Global Assessment of Change.
Subject analysis set title	Opicapone x Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	All subjects of the FAS without any major protocol deviation.

### Primary: Investigator's Global Assessment of Change

End point title	Investigator's Global Assessment of Change <sup>[1]</sup>
End point description:	Investigator's Global Assessment of Change at Visit 4.
End point type	Primary
End point timeframe:	Baseline up to Visit 4

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses have been performed for this primary end point.

End point values	Opicapone x Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	477			
Units: Number of subjects				
number (not applicable)				
Not assessed	3			
Very much improved	31			
Much improved	174			
Minimally improved	135			
No change	88			
Minimally worse	28			
Much worse	15			
Very much worse	3			

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs with onset or worsening after first intake of IMP until trial termination (regularly or premature).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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### Reporting groups

Reporting group title	Opicapone x Safety Set
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Reporting group description:

All subjects who received at least one dose of OPC.

<b>Serious adverse events</b>	Opicapone x Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 495 (6.87%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			

subjects affected / exposed	2 / 495 (0.40%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Inflammation of wound			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ligament sprain			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac disorders</b>			
<b>Arrhythmia</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac failure chronic</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Coronary artery disease</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Tachycardia</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Nervous system disorders</b>			
<b>Dementia</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Dizziness</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Drop attacks</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Freezing phenomenon</b>			

subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Parkinson's disease</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Syncope</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>General disorders and administration site conditions</b>			
<b>Chest pain</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>General physical health deterioration</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Pain</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Gastrointestinal disorders</b>			
<b>Faecal vomiting</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Volvulus</b>			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hallucination, visual			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spondylolisthesis			

subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
Endocarditis			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Opicapone x Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	365 / 495 (73.74%)		
<b>Vascular disorders</b>			
Blood pressure fluctuation			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Hot flush			

subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	7 / 495 (1.41%)		
occurrences (all)	7		
Hypertensive crisis			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	11 / 495 (2.22%)		
occurrences (all)	11		
Orthostatic hypotension			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		
Pallor			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Phlebitis			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Chills			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Crying			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Discomfort			

subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Drug effect decreased			
subjects affected / exposed	11 / 495 (2.22%)		
occurrences (all)	11		
Fatigue			
subjects affected / exposed	15 / 495 (3.03%)		
occurrences (all)	15		
Gait disturbance			
subjects affected / exposed	6 / 495 (1.21%)		
occurrences (all)	6		
Influenza like illness			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		
Medical device site mass			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Medical device site rash			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	2		
Mucosal dryness			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	4 / 495 (0.81%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	11 / 495 (2.22%)		
occurrences (all)	11		
Pyrexia			

subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Seasonal allergy subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Social circumstances Gambling subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 2		
Cough subjects affected / exposed occurrences (all)	7 / 495 (1.41%) 7		
Dry throat subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Dysphonia subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Dyspnoea			

subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Dyspnoea exertional subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Epistaxis subjects affected / exposed occurrences (all)	3 / 495 (0.61%) 3		
Nasal congestion subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 495 (0.61%) 3		
Pharyngeal erythema subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Wheezing subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Psychiatric disorders			
Abnormal behaviour subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Abnormal dreams subjects affected / exposed occurrences (all)	9 / 495 (1.82%) 10		
Affect lability subjects affected / exposed occurrences (all)	3 / 495 (0.61%) 3		
Aggression subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Agitation subjects affected / exposed occurrences (all)	4 / 495 (0.81%) 4		

Anorgasmia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	12 / 495 (2.42%)		
occurrences (all)	12		
Apathy			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	14 / 495 (2.83%)		
occurrences (all)	16		
Depressed mood			
subjects affected / exposed	8 / 495 (1.62%)		
occurrences (all)	8		
Depression			
subjects affected / exposed	18 / 495 (3.64%)		
occurrences (all)	18		
Disinhibition			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Disorientation			
subjects affected / exposed	5 / 495 (1.01%)		
occurrences (all)	5		
Hallucination			
subjects affected / exposed	20 / 495 (4.04%)		
occurrences (all)	24		
Hallucination, auditory			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Hallucination, olfactory			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	2		
Hallucination, visual			
subjects affected / exposed	10 / 495 (2.02%)		
occurrences (all)	13		

Hypersexuality			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Impulse-control disorder			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Initial insomnia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	22 / 495 (4.44%)		
occurrences (all)	25		
Libido increased			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Middle insomnia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Nervousness			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Nightmare			
subjects affected / exposed	5 / 495 (1.01%)		
occurrences (all)	6		
Obsessive-compulsive disorder			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	4		
Paranoia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Persecutory delusion			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Persistent depressive disorder			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		

Rapid eye movement sleep behaviour disorder			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Rapid eye movements sleep abnormal			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	14 / 495 (2.83%)		
occurrences (all)	15		
Sleep attacks			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	11 / 495 (2.22%)		
occurrences (all)	12		
Somnambulism			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Tearfulness			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Product issues			
Device dislocation			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Investigations			
Blood cholesterol increased			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Blood folate decreased			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Blood magnesium decreased			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Blood pressure decreased			

subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Blood pressure increased subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Body temperature increased subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Bone density decreased subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Cardiac murmur subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Heart rate increased subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Lymph node palpable subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Nuclear magnetic resonance imaging abnormal subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Serum ferritin decreased subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Weight decreased subjects affected / exposed occurrences (all)	6 / 495 (1.21%) 6		
Injury, poisoning and procedural complications			
Chest injury subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Concussion			

subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	7 / 495 (1.41%)		
occurrences (all)	8		
Epicondylitis			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Eye injury			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Face injury			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	30 / 495 (6.06%)		
occurrences (all)	45		
Fibula fracture			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Hand fracture			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Head injury			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Humerus fracture			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		
Muscle strain			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Pubis fracture			

<p>subjects affected / exposed occurrences (all)</p> <p>Rib fracture subjects affected / exposed occurrences (all)</p> <p>Scratch subjects affected / exposed occurrences (all)</p> <p>Thermal burn subjects affected / exposed occurrences (all)</p> <p>Upper limb fracture subjects affected / exposed occurrences (all)</p> <p>Wrist fracture subjects affected / exposed occurrences (all)</p>	<p>1 / 495 (0.20%) 1</p> <p>1 / 495 (0.20%) 1</p> <p>2 / 495 (0.40%) 4</p> <p>1 / 495 (0.20%) 1</p> <p>1 / 495 (0.20%) 1</p> <p>1 / 495 (0.20%) 1</p>		
<p>Congenital, familial and genetic disorders</p> <p>Congenital cystic kidney disease subjects affected / exposed occurrences (all)</p>	<p>1 / 495 (0.20%) 1</p>		
<p>Cardiac disorders</p> <p>Palpitations subjects affected / exposed occurrences (all)</p> <p>Tachycardia subjects affected / exposed occurrences (all)</p>	<p>2 / 495 (0.40%) 2</p> <p>1 / 495 (0.20%) 1</p>		
<p>Nervous system disorders</p> <p>Akathisia subjects affected / exposed occurrences (all)</p> <p>Akinesia subjects affected / exposed occurrences (all)</p> <p>Altered state of consciousness</p>	<p>1 / 495 (0.20%) 1</p> <p>1 / 495 (0.20%) 1</p>		

subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Balance disorder			
subjects affected / exposed	6 / 495 (1.21%)		
occurrences (all)	6		
Bradykinesia			
subjects affected / exposed	11 / 495 (2.22%)		
occurrences (all)	12		
Burning feet syndrome			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Carpal tunnel syndrome			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Decreased vibratory sense			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Dementia			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		
Dementia with Lewy bodies			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	29 / 495 (5.86%)		
occurrences (all)	30		
Dizziness postural			
subjects affected / exposed	4 / 495 (0.81%)		
occurrences (all)	4		
Dysarthria			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		
Dysgeusia			

subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Dyskinesia			
subjects affected / exposed	71 / 495 (14.34%)		
occurrences (all)	79		
Dystonia			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Facial paralysis			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Fine motor skill dysfunction			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Freezing phenomenon			
subjects affected / exposed	6 / 495 (1.21%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	13 / 495 (2.63%)		
occurrences (all)	13		
Hyperkinesia			
subjects affected / exposed	6 / 495 (1.21%)		
occurrences (all)	6		
Hyperreflexia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	8 / 495 (1.62%)		
occurrences (all)	8		
Hypokinesia			
subjects affected / exposed	8 / 495 (1.62%)		
occurrences (all)	8		
Memory impairment			
subjects affected / exposed	4 / 495 (0.81%)		
occurrences (all)	4		
Mental impairment			

subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Microsleep			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Myasthenia gravis			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
On and off phenomenon			
subjects affected / exposed	12 / 495 (2.42%)		
occurrences (all)	13		
Orthostatic intolerance			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Orthostatic tremor			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Parkinson's disease			
subjects affected / exposed	8 / 495 (1.62%)		
occurrences (all)	8		
Parkinsonian gait			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Parkinsonism			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Polyneuropathy			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Poor quality sleep			

subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Presyncope subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Psychomotor hyperactivity subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Restless legs syndrome subjects affected / exposed occurrences (all)	8 / 495 (1.62%) 8		
Sciatica subjects affected / exposed occurrences (all)	5 / 495 (1.01%) 6		
Sensory disturbance subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Somnolence subjects affected / exposed occurrences (all)	10 / 495 (2.02%) 10		
Speech disorder subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Syncope subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Tremor subjects affected / exposed occurrences (all)	18 / 495 (3.64%) 18		
Visual field defect subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		

Iron deficiency anaemia subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Ear and labyrinth disorders			
Ear discomfort subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Excessive cerumen production subjects affected / exposed occurrences (all)	3 / 495 (0.61%) 3		
Hypoacusis subjects affected / exposed occurrences (all)	3 / 495 (0.61%) 3		
Tinnitus subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Vertigo subjects affected / exposed occurrences (all)	6 / 495 (1.21%) 7		
Vertigo positional subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Eye disorders			
Astigmatism subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Blepharitis subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Cataract subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Diplopia			

subjects affected / exposed occurrences (all)	4 / 495 (0.81%) 4		
Dry eye subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Eye movement disorder subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Eyelid oedema subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Lacrimation increased subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Saccadic eye movement subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Vision blurred subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Visual impairment subjects affected / exposed occurrences (all)	4 / 495 (0.81%) 5		
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Abdominal distension subjects affected / exposed occurrences (all)	3 / 495 (0.61%) 3		
Abdominal pain subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Abdominal pain upper subjects affected / exposed occurrences (all)	10 / 495 (2.02%) 12		

Aptyalism			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	43 / 495 (8.69%)		
occurrences (all)	47		
Diarrhoea			
subjects affected / exposed	13 / 495 (2.63%)		
occurrences (all)	14		
Dry mouth			
subjects affected / exposed	40 / 495 (8.08%)		
occurrences (all)	45		
Dyspepsia			
subjects affected / exposed	4 / 495 (0.81%)		
occurrences (all)	4		
Dysphagia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Epigastric discomfort			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Eructation			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	4 / 495 (0.81%)		
occurrences (all)	4		
Gastric mucosa erythema			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Gastritis erosive			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		

Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	4 / 495 (0.81%) 4		
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Lip swelling subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Nausea subjects affected / exposed occurrences (all)	35 / 495 (7.07%) 38		
Oesophagitis subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Oral pain subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Saliva discolouration subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Salivary hypersecretion subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Vomiting subjects affected / exposed occurrences (all)	8 / 495 (1.62%) 8		
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Hepatic cyst subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Skin and subcutaneous tissue disorders			

Actinic keratosis			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Hand dermatitis			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	9 / 495 (1.82%)		
occurrences (all)	9		
Night sweats			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		
Pigmentation disorder			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Psoriasis			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	4 / 495 (0.81%)		
occurrences (all)	4		
Rash pruritic			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Rosacea			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Skin irritation			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		

Skin striae subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Renal and urinary disorders			
Chromaturia subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Incontinence subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Micturition urgency subjects affected / exposed occurrences (all)	4 / 495 (0.81%) 4		
Nocturia subjects affected / exposed occurrences (all)	5 / 495 (1.01%) 5		
Pollakiuria subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Polyuria subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Renal cyst subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Urge incontinence subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Urinary incontinence subjects affected / exposed occurrences (all)	3 / 495 (0.61%) 3		
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	7 / 495 (1.41%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	16 / 495 (3.23%)		
occurrences (all)	16		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Joint swelling			
subjects affected / exposed	4 / 495 (0.81%)		
occurrences (all)	4		
Limb discomfort			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Mobility decreased			
subjects affected / exposed	11 / 495 (2.22%)		
occurrences (all)	12		
Muscle rigidity			
subjects affected / exposed	11 / 495 (2.22%)		
occurrences (all)	13		
Muscle spasms			
subjects affected / exposed	13 / 495 (2.63%)		
occurrences (all)	14		
Muscle tightness			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Muscle twitching			
subjects affected / exposed	5 / 495 (1.01%)		
occurrences (all)	6		
Muscular weakness			
subjects affected / exposed	4 / 495 (0.81%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		

Musculoskeletal stiffness subjects affected / exposed occurrences (all)	5 / 495 (1.01%) 5		
Myalgia subjects affected / exposed occurrences (all)	4 / 495 (0.81%) 4		
Neck pain subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Osteoarthritis subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Osteochondrosis subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Osteoporosis subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Pain in extremity subjects affected / exposed occurrences (all)	12 / 495 (2.42%) 14		
Rheumatoid arthritis subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Spinal column stenosis subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Spinal pain subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Tendonitis subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Infections and infestations Angular cheilitis			

subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Bronchitis subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Candida infection subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Cellulitis subjects affected / exposed occurrences (all)	3 / 495 (0.61%) 3		
Chronic sinusitis subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Cystitis subjects affected / exposed occurrences (all)	5 / 495 (1.01%) 5		
Eye infection subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Gastroenteritis rotavirus subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Gastrointestinal infection subjects affected / exposed occurrences (all)	4 / 495 (0.81%) 4		
Influenza subjects affected / exposed occurrences (all)	3 / 495 (0.61%) 4		
Lower respiratory tract infection subjects affected / exposed occurrences (all)	3 / 495 (0.61%) 3		
Nasopharyngitis			

subjects affected / exposed occurrences (all)	19 / 495 (3.84%) 20		
Onychomycosis subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Pulpitis dental subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Respiratory tract infection subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
Tooth infection subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 495 (1.41%) 9		
Viral infection subjects affected / exposed occurrences (all)	2 / 495 (0.40%) 2		
<b>Metabolism and nutrition disorders</b>			
Abnormal loss of weight subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		
Decreased appetite subjects affected / exposed occurrences (all)	5 / 495 (1.01%) 5		
Diabetes mellitus subjects affected / exposed occurrences (all)	1 / 495 (0.20%) 1		

Food craving			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Gout			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Hypovolaemia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Magnesium deficiency			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Vitamin B12 deficiency			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Vitamin D deficiency			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2016	Global Protocol Amendment No. 1, DE
20 September 2016	Global Protocol Amendment No. 1, UK
03 November 2016	Global Protocol Amendment No. 2, UK
20 December 2016	Global Protocol Amendment No. 2, DE
20 December 2016	Global Protocol Amendment No. 3, UK
20 September 2017	Global Protocol Amendment No. 4, UK
17 October 2017	Global Protocol Amendment No. 3, DE

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported