



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
Public contact	André Garrido, BIAL - Portela & C ^a , S.A., 00351 229866100, andre.garrido@bial.com
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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 ≥ 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.

Number of subjects in period 1^[1]	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

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
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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 ^[1]
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

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.

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

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

Non-serious adverse events	Opicapone x Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	365 / 495 (73.74%)		
Vascular disorders			
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	2 / 495 (0.40%)		
occurrences (all)	2		
Dyspnoea exertional			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		
Nasal congestion			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		
Pharyngeal erythema			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Abnormal dreams			
subjects affected / exposed	9 / 495 (1.82%)		
occurrences (all)	10		
Affect lability			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		
Aggression			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Agitation			
subjects affected / exposed	4 / 495 (0.81%)		
occurrences (all)	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	1 / 495 (0.20%)		
occurrences (all)	1		
Blood pressure increased			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Bone density decreased			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Cardiac murmur			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Heart rate increased			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Lymph node palpable			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Nuclear magnetic resonance imaging abnormal			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Serum ferritin decreased			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	6 / 495 (1.21%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	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			

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

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	1 / 495 (0.20%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Psychomotor hyperactivity			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Restless legs syndrome			
subjects affected / exposed	8 / 495 (1.62%)		
occurrences (all)	8		
Sciatica			
subjects affected / exposed	5 / 495 (1.01%)		
occurrences (all)	6		
Sensory disturbance			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	10 / 495 (2.02%)		
occurrences (all)	10		
Speech disorder			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	18 / 495 (3.64%)		
occurrences (all)	18		
Visual field defect			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	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	4 / 495 (0.81%)		
occurrences (all)	4		
Dry eye			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Eye movement disorder			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Eyelid oedema			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Lacrimation increased			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Saccadic eye movement			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	4 / 495 (0.81%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 495 (0.20%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	3 / 495 (0.61%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	2 / 495 (0.40%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	10 / 495 (2.02%)		
occurrences (all)	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		

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

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported