Clinical trial results:
TOLEDO Multicenter, parallel-group, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of apomorphine subcutaneous infusion in Parkinson's disease patients with motor complications not well controlled on medical treatment

Summary

EudraCT number	2013-000980-10
Trial protocol	AT DE ES FR DK NL
Global end of trial date	08 June 2017

Results information

Result version number	v1 (current)
This version publication date	28 November 2018
First version publication date	28 November 2018

Trial information

Trial identification

Sponsor protocol code	CT-37527-13-0124

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02006121
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Britannia Pharmaceuticals Ltd
Sponsor organisation address	200 Longwater Avenue, Green Park, Reading, United Kingdom, RG2 6GP
Public contact	Clinical Operations, Britannia Pharmaceuticals Ltd, +44 01635 568400,
Scientific contact	Clinical Operations, Britannia Pharmaceuticals Ltd, +44 01635 568400,

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	11 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 June 2016
Global end of trial reached?	Yes
Global end of trial date	08 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to investigate the efficacy of apomorphine subcutaneous infusion compared to placebo in PD patients with motor fluctuations not well controlled on medical treatment.

Protection of trial subjects:

The abdominal skin must be checked at each visit. Any skin changes must be documented (counted and described).

Before starting the infusion and at each visit, patients are to be reminded of strict hygiene, massages after removing the needle, rotation of insertion site, making use of the whole abdomen (if comfortable to the patient), do not leave needle in for >18 hours.

If nodule formation is suspected to interfere with the absorption of the study drug, patients should be re-trained in identifying suitable insertion sites. When necessary and depending on local availability, the following additional methods are permitted:
-ultrasound,
-silicone patches or
-massage devices including creams, as recommended by the national provider of apomorphine or by national treatment guidelines.

Laboratory tests are performed at Screening, Baseline (V3) and at V6, V8 and V10 and during open-label V12, V13, V14 and V15. These will include full blood count with differential blood count, haptoglobin, bilirubin and LDH.

In the case of a drop of hemoglobin by ≥1.5 g/dl compared to the previous test, hemolytic anemia must be ruled out. The urgency of intervention depends on the degree of the change and whether there are any concomitant laboratory changes suggestive of hemolytic anemia and must be judged by the investigator in charge of reviewing the blood test results.

The patient must be asked to come for an unscheduled safety visit and have the following assessments:
-clinical assessment for symptoms and signs of anemia,
-full blood count with differential blood count,
-Coombs test,
-haptoglobin,
-bilirubin,
-LDH.
If any findings suggest hemolytic anemia, an internist / hematologist must be consulted. If hemolytic anemia is confirmed, apomorphine must be stopped and the patient must be managed as advised by the consulted internist / hematologist. The patient must be discontinued from the study.

Background therapy:

Antiemetic premedication administered according to local standards. Recommended pre-treatment use of domperidone was 10 mg TID starting 3 days prior to the infusion.

Evidence for comparator:

N/A

Actual start date of recruitment	03 March 2014
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	Netherlands: 14
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 20
Worldwide total number of subjects	107
EEA total number of subjects	107

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)	56
From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

There were 128 patients screened and 107 patients randomized across 23 study centres in 7 countries (Austria, Denmark, France, Germany, Netherlands, Spain and UK). Patients were enrolled between 03-Mar-2014 and 01-Mar-2016.

Pre-assignment

Screening details:

Following a consent discussion and written informed consent, the patients entered a screening period for up to 21 days, which allowed washout of any contraindicated medications and the stabilization of existing medications.

Period 1

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

Blinding implementation details:

A centralised randomisation was performed for the DBP. The random allocation of treatments to patients was done by the Biometrics Department of AMS according to their SOP. Three sets of sealed randomisation envelopes were prepared, which were to be stored securely unopened until after database lock for the DBP of the study): one copy was held by AMS drug safety, one copy by STADA drug safety, and the final set was distributed to Investigative sites.

Arms

Are arms mutually exclusive?	Yes
Arm title	Apomorphine hydrochloride

Arm description:

Apomorphine hydrochloride 5 mg/ml solution for infusion in pre-filled syringe

Arm type	Experimental
Investigational medicinal product name	Apomorphine hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The starting dose for apomorphine subcutaneous infusion was 1 mg/hour during the first day of infusion. If no adverse effects occurred, the hourly flow rate was then be increased in the following manner:

>By 0.5 to 1 mg/hour each day, until the end of Visit 3 or until the maximum dose of 8 mg/hour or the highest tolerated hourly dose has been reached, whichever occurs first.

>At the weekly visits up to week 4 (V6): by 0.5 to 1 mg/hour per visit until the maximum dose of 8 mg/hour or the highest tolerated hourly dose has been reached, whichever occurs first.

Arm title	Placebo

Arm description:

Placebo saline infusion

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The starting dose for placebo will be 1 mg/hour during the first day of infusion.

If no adverse effects occur, the hourly flow rate will then be increased in the following manner:

>By 0.5 to 1 mg/hour each day, until the end of Visit 3 or until the maximum dose of 8 mg/hour or the highest tolerated hourly dose has been reached, whichever occurs first.

>At the weekly visits up to week 4 (V6): by 0.5 to 1 mg/hour per visit until the maximum dose of 8 mg/hour or the highest tolerated hourly dose has been reached, whichever occurs first

Number of subjects in period 1	Apomorphine hydrochloride	Placebo
Started	54	53
Completed	42	29
Not completed	12	24
Consent withdrawn by subject	3	4
Adverse event, non-fatal	6	-
Non-compliance with study drug	1	3
Target infusion rate was poorly tolerated	1	-
Inconvenience of the infusion system	-	1
Lack of efficacy	1	16

Period 2

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

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Apomorphine continued treatment in OLP

Arm description:

Continued OLP treatment of apomorphine hydrochloride 5 mg/ml solution for infusion in pre-filled syringe

Arm type	Experimental

Investigational medicinal product name	Apomorphine hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The starting dose for apomorphine subcutaneous infusion was 1 mg/hour during the first day of infusion. If no adverse effects occurred, the hourly flow rate was then be increased in the following manner:

>By 0.5 to 1 mg/hour each day, until the end of Visit 3 or until the maximum dose of 8 mg/hour or the highest tolerated hourly dose has been reached, whichever occurs first.

>At the weekly visits up to week 4 (V6): by 0.5 to 1 mg/hour per visit until the maximum dose of 8 mg/hour or the highest tolerated hourly dose has been reached, whichever occurs first.

Arm title	Apomorphine naive

Arm description:

Apomorphine OLP treatment for those who received placebo in the DBP.

Arm type	Experimental
Investigational medicinal product name	Apomorphine hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The starting dose for apomorphine subcutaneous infusion was 1 mg/hour during the first day of infusion. If no adverse effects occurred, the hourly flow rate was then be increased in the following manner:

>By 0.5 to 1 mg/hour each day, until the end of Visit 3 or until the maximum dose of 8 mg/hour or the highest tolerated hourly dose has been reached, whichever occurs first.

>At the weekly visits up to week 4 (V6): by 0.5 to 1 mg/hour per visit until the maximum dose of 8 mg/hour or the highest tolerated hourly dose has been reached, whichever occurs first.

Number of subjects in period 2[1]	Apomorphine continued treatment in OLP	Apomorphine naive
Started	40	29
Completed	30	29
Not completed	10	15
Consent withdrawn by subject	3	-
Adverse event, non-fatal	4	11
Non-compliance with study drug	-	3
Lack of efficacy	2	-
Protocol deviation	1	1
Joined	0	15
Early switched to OLP from Placebo DBP	-	15

Notes:

[1] - 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: A total of 71 subjects completed the Double-Blind Phase. However, 84 subjects started the Open-Label Phase as subjects that did not complete the Double-Blind Phase were still eligible to take part in the Open-Label Phase part of the study. Two subjects that received apomorphine and completed the Double-Blind Phase did not join the Open-Label Phase part of the study. Fifteen subjects that received placebo in the Double-Blind Phase switched to the Open-Label Phase early.

Baseline characteristics

Reporting groups	
Reporting group title	Apomorphine hydrochloride
Reporting group description:	
Apomorphine hydrochloride 5 mg/ml solution for infusion in pre-filled syringe	
Reporting group title	Placebo
Reporting group description:	
Placebo saline infusion	

Reporting group values	Apomorphine hydrochloride	Placebo	Total
Number of subjects	54	53	107
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	27	29	56
From 65-84 years	27	24	51
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.3	62.9	
standard deviation	± 9.4	± 8.4	-
Gender categorical Units: Subjects			
Female	19	22	41
Male	35	31	66

Subject analysis sets	
Subject analysis set title	mITT analysis set - apomorphine
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomised patients treated at least once with the study medication and had at least one post baseline observation for the primary endpoint.	
Subject analysis set title	mITT analysis set - placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomised patients treated at least once with placebo and had at least one post baseline observation for the primary endpoint.	

Reporting group values	mITT analysis set - apomorphine	mITT analysis set - placebo	
Number of subjects	53	52	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	26	28	
From 65-84 years	27	24	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	63.6	63.2	
standard deviation	± 9.3	± 8.3	
Gender categorical Units: Subjects			
Female	19	20	
Male	34	32	

End points

End points reporting groups

Reporting group title	Apomorphine hydrochloride
Reporting group description:	
Apomorphine hydrochloride 5 mg/ml solution for infusion in pre-filled syringe	
Reporting group title	Placebo
Reporting group description:	
Placebo saline infusion	
Reporting group title	Apomorphine continued treatment in OLP
Reporting group description:	
Continued OLP treatment of apomorphine hydrochloride 5 mg/ml solution for infusion in pre-filled syringe	
Reporting group title	Apomorphine naive
Reporting group description:	
Apomorphine OLP treatment for those who received placebo in the DBP.	
Subject analysis set title	mITT analysis set - apomorphine
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomised patients treated at least once with the study medication and had at least one post baseline observation for the primary endpoint.	
Subject analysis set title	mITT analysis set - placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomised patients treated at least once with placebo and had at least one post baseline observation for the primary endpoint.	

Primary: Change in time spent "OFF"

End point title	Change in time spent "OFF"
End point description:	
Primary efficacy variable is the absolute change in time spent “OFF” from baseline (start of blinded treatment) to the end of 12 weeks double-blind treatment period based on patient diaries using MMRM mITT population. The mean reduction (improvement) of absolute 'OFF' time as reported by the patient using the Hauser diary.	
End point type	Primary
End point timeframe:	
From baseline to the end of 12 weeks double-blind treatment period.	

End point values	mITT analysis set - apomorphine	mITT analysis set - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	52		
Units: hour				
least squares mean (confidence interval 95%)	-2.61 (-3.43 to -1.80)	-0.75 (-1.66 to 0.16)		

Statistical analyses

Statistical analysis title	Superiority test for change in time spent "OFF"
Comparison groups	mITT analysis set - apomorphine v mITT analysis set - placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Patient Global Impression of Change

End point title	Patient Global Impression of Change

End point description:

A self-administered questionnaire (Patient Global Impression of Change) measuring personal general state of health since the start of the study.

End point type	Secondary

End point timeframe:

Change was measured from baseline to end of 12 weeks treatment period.

End point values	mITT analysis set - apomorphine	mITT analysis set - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	52		
Units: % patients at least minimal improvement				
number (not applicable)	79.1	23.5		

Statistical analyses

Statistical analysis title	Superiority test for PGIC

Statistical analysis description:

At the end of 12 weeks' double blind treatment 79.1% of apomorphine treated patients reported at least a minimal improvement in their general health state (using PGIC) compared with 23.5% of placebo-treated patients (p<0.0001).

Comparison groups	mITT analysis set - apomorphine v mITT analysis set - placebo

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in time spent "ON" without troublesome dyskinesia

End point title	Change in time spent "ON" without troublesome dyskinesia

End point description:

Change in time spent "ON" without troublesome dyskinesia over 24 hours at the End of the Double-Blind Phase (Visit 10) from Baseline. Measurement based on Patient Diaries Using MMRM mITT Population. The mean change in 'ON' time as reported by the patient using the Hauser diary.

End point type	Secondary

End point timeframe:

Change was measured from baseline to end of the 12 weeks treatment period.

End point values	mITT analysis set - apomorphine	mITT analysis set - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	52		
Units: hours				
least squares mean (confidence interval 95%)	2.90 (2.07 to 3.73)	0.85 (-0.09 to 1.78)		

Statistical analyses

Statistical analysis title	Superiority test for change in time spent "ON"
Comparison groups	mITT analysis set - apomorphine v mITT analysis set - placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022 [1]
Method	Fisher exact

Notes:

[1] - The LS mean difference between the treatment groups was 2.05 hours (0.74, 3.36) (p=0.0022)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected on an on-going basis from the day of written informed consent until the last patient visit required by the protocol.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo DBP
Reporting group description: -	
Reporting group title	Apomorphine DBP
Reporting group description: -	
Reporting group title	Apomorphine naive in OLP
Reporting group description: -	
Reporting group title	Apomorphine continued treatment in OLP

Reporting group description: -

Serious adverse events	Placebo DBP	Apomorphine DBP	Apomorphine naive in OLP
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 53 (3.77%)	5 / 54 (9.26%)	9 / 44 (20.45%)
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)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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
Lymphoma			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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			
Hypotension			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (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
Surgical and medical procedures			
Deep brain stimulation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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			
Infusion site extravasation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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
Chest pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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			
Pulmonary embolism			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (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
Depression			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (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
Paranoia			

subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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
Delirium			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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
Product issues			
Device difficult to use			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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			
Eosinophil count decreased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (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
Haematocrit decreased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (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
Haemoglobin decreased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (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
Red blood cell count decreased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Forearm fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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
Lower limb fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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
Radius fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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 disorders			
Angina pectoris			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (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
Nervous system disorders			
On and off phenomenon			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroleptic malignant syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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

Parkinson's disease			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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
Radicular syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (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
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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 disorder			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (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
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (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
Constipation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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
Diarrhoea			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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 haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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			
Cholelithiasis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (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			
Infusion site cellulitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Apomorphine continued treatment in OLP		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 40 (27.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphoma			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Deep brain stimulation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Infusion site extravasation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paranoia			

subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Delirium				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device difficult to use				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Eosinophil count decreased				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematocrit decreased				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Red blood cell count decreased				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Forearm fracture				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina pectoris				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
On and off phenomenon				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carotid artery stenosis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuroleptic malignant syndrome				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Parkinson's disease			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radicular syndrome			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood disorder			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infusion site cellulitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo DBP	Apomorphine DBP	Apomorphine naive in OLP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 53 (56.60%)	50 / 54 (92.59%)	43 / 44 (97.73%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Lung neoplasm malignant			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Lymphoma			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Metastases to liver			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Skin papilloma			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			

Haematoma			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	1 / 53 (1.89%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	1	1	0
Hypotension			
subjects affected / exposed	0 / 53 (0.00%)	4 / 54 (7.41%)	0 / 44 (0.00%)
occurrences (all)	0	4	0
Orthostatic hypotension			
subjects affected / exposed	1 / 53 (1.89%)	2 / 54 (3.70%)	3 / 44 (6.82%)
occurrences (all)	1	2	3
Surgical and medical procedures			
Deep brain stimulation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 53 (1.89%)	4 / 54 (7.41%)	2 / 44 (4.55%)
occurrences (all)	1	4	2
Infusion site bruising			
subjects affected / exposed	1 / 53 (1.89%)	3 / 54 (5.56%)	0 / 44 (0.00%)
occurrences (all)	1	3	0
Infusion site erythema			
subjects affected / exposed	2 / 53 (3.77%)	9 / 54 (16.67%)	5 / 44 (11.36%)
occurrences (all)	2	9	5
Infusion site haematoma			
subjects affected / exposed	5 / 53 (9.43%)	3 / 54 (5.56%)	0 / 44 (0.00%)
occurrences (all)	5	3	0
Infusion site inflammation			
subjects affected / exposed	0 / 53 (0.00%)	3 / 54 (5.56%)	0 / 44 (0.00%)
occurrences (all)	0	3	0
Infusion site nodule			
subjects affected / exposed	0 / 53 (0.00%)	24 / 54 (44.44%)	21 / 44 (47.73%)
occurrences (all)	0	24	21
Infusion site pruritus			

subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Infusion site swelling			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	0 / 53 (0.00%)	5 / 54 (9.26%)	0 / 44 (0.00%)
occurrences (all)	0	5	0
Asthenia			
subjects affected / exposed	0 / 53 (0.00%)	4 / 54 (7.41%)	0 / 44 (0.00%)
occurrences (all)	0	4	0
Chest pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Feeling abnormal			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Gait disturbance			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Infusion site discolouration			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Infusion site extravasation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Infusion site haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Infusion site hypersensitivity			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	2 / 44 (4.55%)
occurrences (all)	0	1	2
Infusion site induration			

subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Infusion site irritation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Infusion site oedema			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Infusion site pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Infusion site rash			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Infusion site reaction			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	2
Medical device pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Nodule			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	2
Pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	2
Peripheral swelling			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Vessel puncture site bruise			

subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Pruritus genital			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 53 (1.89%)	3 / 54 (5.56%)	0 / 44 (0.00%)
occurrences (all)	1	3	0
Dyspnoea			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Pulmonary embolism			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Tachypnoea			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Adjustment disorder with depressed mood			

subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Binge eating			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	2 / 53 (3.77%)	1 / 54 (1.85%)	3 / 44 (6.82%)
occurrences (all)	2	1	3
Delirium			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	1 / 53 (1.89%)	2 / 54 (3.70%)	3 / 44 (6.82%)
occurrences (all)	1	2	3
Disturbance in sexual arousal			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Hallucination			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	3 / 44 (6.82%)
occurrences (all)	0	1	3
Hallucination, visual			
subjects affected / exposed	2 / 53 (3.77%)	1 / 54 (1.85%)	4 / 44 (9.09%)
occurrences (all)	2	1	4
Hypersexuality			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Illusion			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Impulse-control disorder			

subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 53 (1.89%)	6 / 54 (11.11%)	6 / 44 (13.64%)
occurrences (all)	1	6	6
Middle insomnia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Nightmare			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Panic attack			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Paranoia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Parasomnia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Psychotic disorder			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Rapid eye movements sleep abnormal			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Restlessness			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Sleep disorder			
subjects affected / exposed	1 / 53 (1.89%)	1 / 54 (1.85%)	3 / 44 (6.82%)
occurrences (all)	1	1	3
Stereotypy			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	0 / 44 (0.00%)
occurrences (all)	0	2	0

Suicidal ideation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Product issues			
Device connection issue			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Device difficult to use			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Needle issue			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Blood pressure orthostatic			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
electrocardiogram q wave abnormal			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
electrocardiogram qt prolonged			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Eosinophil count decreased			

subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Haematocrit decreased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Inspiratory capacity decreased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Neutrophil count increased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Oxygen saturation decreased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Red blood cell count decreased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 53 (9.43%)	4 / 54 (7.41%)	8 / 44 (18.18%)
occurrences (all)	5	4	8
Contusion			

subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Eye contusion			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Forearm fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Hand fracture			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Incorrect dose administered			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Laceration			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Lower limb fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Muscle rupture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Radius fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Skin wound			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Spinal compression fracture			

subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Traumatic haematoma			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Upper limb fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Aortic valve incompetence			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Bundle branch block left			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Myocardial infarction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Postural orthostatic tachycardia syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Akinesia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Autonomic nervous system imbalance			

subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Carotid artery stenosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Carpal tunnel syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Cervicobrachial syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Chorea			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Dementia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Disturbance in attention			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	2 / 53 (3.77%)	5 / 54 (9.26%)	4 / 44 (9.09%)
occurrences (all)	2	5	4
Dysarthria			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Dyskinesia			
subjects affected / exposed	0 / 53 (0.00%)	8 / 54 (14.81%)	5 / 44 (11.36%)
occurrences (all)	0	8	5
Dystonia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	2 / 53 (3.77%)	7 / 54 (12.96%)	3 / 44 (6.82%)
occurrences (all)	2	7	3
Hypersomnia			

subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Memory impairment			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Motor dysfunction			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Neuralgia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Neuroleptic malignant syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
On and off phenomenon			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	2 / 44 (4.55%)
occurrences (all)	1	0	2
Orthostatic intolerance			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Parkinson's disease			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Poor quality sleep			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Radicular syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Restless legs syndrome			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Sciatica			

subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	2 / 44 (4.55%)
occurrences (all)	0	2	2
Sensory disturbance			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	2 / 53 (3.77%)	12 / 54 (22.22%)	6 / 44 (13.64%)
occurrences (all)	2	12	6
Syncope			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Unresponsive to stimuli			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 53 (0.00%)	3 / 54 (5.56%)	2 / 44 (4.55%)
occurrences (all)	0	3	2
Anaemia			
subjects affected / exposed	1 / 53 (1.89%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	1	1	0
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Blood disorder			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Haemolytic anaemia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0

Lymphopenia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Inner ear inflammation			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Conjunctival haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Diplopia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Eyelid haematoma			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Metamorphopsia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Visual impairment			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 53 (5.66%)	4 / 54 (7.41%)	2 / 44 (4.55%)
occurrences (all)	3	4	2
Nausea			
subjects affected / exposed	5 / 53 (9.43%)	12 / 54 (22.22%)	7 / 44 (15.91%)
occurrences (all)	5	12	7
Salivary hypersecretion			

subjects affected / exposed	1 / 53 (1.89%)	1 / 54 (1.85%)	2 / 44 (4.55%)
occurrences (all)	1	1	2
Vomiting			
subjects affected / exposed	2 / 53 (3.77%)	4 / 54 (7.41%)	3 / 44 (6.82%)
occurrences (all)	2	4	3
Abdominal pain			
subjects affected / exposed	1 / 53 (1.89%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	1	1	0
Colitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	2 / 53 (3.77%)	2 / 54 (3.70%)	0 / 44 (0.00%)
occurrences (all)	2	2	0
Dry mouth			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	1 / 53 (1.89%)	1 / 54 (1.85%)	2 / 44 (4.55%)
occurrences (all)	1	1	2
Gastritis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Haematemesis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Umbilical hernia			

subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Jaundice			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Decubitus ulcer			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	1 / 53 (1.89%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	1	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Intertrigo			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Pigmentation disorder			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Rash			

subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	1	1	0
Toxic skin eruption			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Micturition urgency			
subjects affected / exposed	0 / 53 (0.00%)	3 / 54 (5.56%)	0 / 44 (0.00%)
occurrences (all)	0	3	0
Pollakiuria			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Polyuria			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Urge incontinence			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Genital rash			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Cushingoid			

subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	2 / 44 (4.55%)
occurrences (all)	0	2	2
Axillary mass			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	3 / 44 (6.82%)
occurrences (all)	1	0	3
Bursitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Camptocormia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Facet joint syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Haemarthrosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Muscle spasms			

subjects affected / exposed	0 / 53 (0.00%)	3 / 54 (5.56%)	1 / 44 (2.27%)
occurrences (all)	0	3	1
Musculoskeletal pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 53 (1.89%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	1	1	0
Myalgia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	2
Neck pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Osteitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Osteoarthritis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Osteoporosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	2 / 53 (3.77%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	2	0	1
Pathological fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Plantar fasciitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Spinal osteoarthritis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Spinal pain			

subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Synovitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Tendon pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Tendonitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Cystitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Gastrointestinal infection			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Hordeolum			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Infective tenosynovitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Infusion site cellulitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1

Nasopharyngitis			
subjects affected / exposed	3 / 53 (5.66%)	3 / 54 (5.56%)	1 / 44 (2.27%)
occurrences (all)	3	3	1
Oral herpes			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Pneumonia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Pyelonephritis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	1 / 53 (1.89%)	3 / 54 (5.56%)	3 / 44 (6.82%)
occurrences (all)	1	3	3
Urosepsis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Hyperphagia			

subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Increased appetite			
subjects affected / exposed	0 / 53 (0.00%)	0 / 54 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Vitamin B12 deficiency			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	0 / 44 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Apomorphine continued treatment in OLP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 40 (95.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Lung neoplasm malignant			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Lymphoma			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Metastases to liver			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Skin papilloma			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hypertension			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Orthostatic hypotension			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Surgical and medical procedures			
Deep brain stimulation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Infusion site bruising			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Infusion site erythema			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Infusion site haematoma			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Infusion site inflammation			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Infusion site nodule			
subjects affected / exposed	12 / 40 (30.00%)		
occurrences (all)	12		
Infusion site pruritus			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Infusion site swelling			

subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Oedema peripheral				
subjects affected / exposed	4 / 40 (10.00%)			
occurrences (all)	4			
Asthenia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Chest pain				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Feeling abnormal				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Gait disturbance				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Influenza like illness				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Infusion site discolouration				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Infusion site extravasation				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Infusion site haemorrhage				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Infusion site hypersensitivity				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Infusion site induration				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Infusion site irritation				

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Infusion site oedema			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Infusion site pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Infusion site rash			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Infusion site reaction			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Medical device pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Nodule			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Vessel puncture site bruise			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Pruritus genital			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Pulmonary embolism			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Tachypnoea			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Anxiety			

subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Binge eating				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Confusional state				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Delirium				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Depressed mood				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Depression				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Disturbance in sexual arousal				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Hallucination				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Hallucination, visual				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Hypersexuality				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Illusion				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Impulse-control disorder				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Insomnia				

subjects affected / exposed	4 / 40 (10.00%)			
occurrences (all)	4			
Middle insomnia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Nightmare				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Panic attack				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Paranoia				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Parasomnia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Psychotic disorder				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Rapid eye movements sleep abnormal				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Restlessness				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Sleep disorder				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Stereotypy				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Suicidal ideation				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			

Product issues			
Device connection issue			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Device difficult to use			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Needle issue			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Blood pressure orthostatic			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
electrocardiogram q wave abnormal			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
electrocardiogram qt prolonged			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Eosinophil count decreased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Haematocrit decreased			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Inspiratory capacity decreased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Neutrophil count increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Oxygen saturation decreased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Red blood cell count decreased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
White blood cell count increased			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Contusion			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Eye contusion			

subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Forearm fracture				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Hand fracture				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Incorrect dose administered				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Laceration				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Ligament sprain				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Lower limb fracture				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Muscle rupture				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Radius fracture				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Skin abrasion				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Skin wound				
subjects affected / exposed	3 / 40 (7.50%)			
occurrences (all)	3			
Spinal compression fracture				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Traumatic haematoma				

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Upper limb fracture			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Aortic valve incompetence			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Bundle branch block left			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Myocardial infarction			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Postural orthostatic tachycardia syndrome			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Akinesia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Autonomic nervous system imbalance			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Carotid artery stenosis			

subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Carpal tunnel syndrome				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Cervicobrachial syndrome				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Chorea				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Dementia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Disturbance in attention				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Dizziness				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Dysarthria				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Dyskinesia				
subjects affected / exposed	5 / 40 (12.50%)			
occurrences (all)	5			
Dystonia				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Headache				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Hypersomnia				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Lethargy				

subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Memory impairment				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Motor dysfunction				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Neuralgia				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Neuroleptic malignant syndrome				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
On and off phenomenon				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Orthostatic intolerance				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Parkinson's disease				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Poor quality sleep				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Radicular syndrome				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Restless legs syndrome				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Sciatica				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Sensory disturbance				

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Syncope			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Unresponsive to stimuli			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Blood disorder			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Haemolytic anaemia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Iron deficiency anaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Lymphopenia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		

Ear and labyrinth disorders			
Inner ear inflammation			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Conjunctival haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Diplopia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Eyelid haematoma			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Metamorphopsia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Visual impairment			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Salivary hypersecretion			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Vomiting			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Colitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Dry mouth			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Haematemesis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Umbilical hernia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Jaundice			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Decubitus ulcer			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Dermatitis contact			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Intertrigo			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Pigmentation disorder			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Seborrhoeic dermatitis			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Toxic skin eruption			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Micturition urgency			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Polyuria			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Urge incontinence			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Urinary retention			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Genital rash			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Cushingoid			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Arthralgia				
subjects affected / exposed	3 / 40 (7.50%)			
occurrences (all)	3			
Axillary mass				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Back pain				
subjects affected / exposed	3 / 40 (7.50%)			
occurrences (all)	3			
Bursitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Camptocormia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Facet joint syndrome				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Haemarthrosis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Intervertebral disc protrusion				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Joint swelling				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Lumbar spinal stenosis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Muscle spasms				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Musculoskeletal pain				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			

Musculoskeletal stiffness				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Myalgia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Neck pain				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Osteitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Osteoarthritis				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Osteoporosis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Pain in extremity				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Pathological fracture				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
Plantar fasciitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Spinal osteoarthritis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Spinal pain				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences (all)	0			
Synovitis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			

Tendon pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Hordeolum			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Infective tenosynovitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Infusion site cellulitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Oral herpes			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Pyelonephritis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Urosepsis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hypernatraemia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Hyperphagia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		

Increased appetite subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Vitamin B12 deficiency subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2013	Substantial global protocol amendment to version 2.0, dated 30-Sep-2013. Summary of changes Modification 1: New inclusion criteria added according to the BfArM deficiency letter dated 09 Sep 2013 Modification 2: Clarification that the current version of the PD Sleep Scale (PDSS-2) will be used and update of the corresponding reference Modification 3: Administrative change to account for the fact that SAEs will be forwarded automatically via eCRF. Fax numbers should only be used in case of a technical failure or for additional information to be sent Modification 4: Correction of wording to comply with current legislation Modification 5: To update the wording concerning SAE reporting period to follow current EU legislation
20 August 2014	Substantial global protocol amendment to version 3.0, dated 02-Jul-2014. Summary of changes Modification 1: Change of Sponsor and Responsibilities Change of Sponsor from STADA Arzneimittel AG Germany to the Marketing Authorization holder Britannia Pharmaceuticals Limited. Modification 2: Prolongation of Open Label Follow-up The open label follow-up phase has been prolonged from 9 to 12 months including an increase in visit numbers during open label treatment from 4 to 5 visits and addition of 4 interim telephone contacts. The long-term follow up is now referred to as open label treatment throughout the document. Modification 3: Safety Parameters Addition of new safety questionnaire Columbia Suicide-Severity Rating Scale (C-SSRS), additional question referring to sleep episodes and orthostatic blood pressure measurement. Modification 4: Procedures Introduction of day-case hospitalization for the titration visit 3 (week 1), provided that a minimum of 8 hours daily stay can be ensured.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30055903