Clinical trial results:
Open-Label Safety Study of ADS-5102 (Amantadine HCl) Extended Release Capsules for the Treatment of Levodopa-Induced Dyskinesia

Summary

EudraCT number	2014-003739-20
Trial protocol	DE ES AT FR
Global end of trial date	28 February 2018

Results information

Result version number	v1 (current)
This version publication date	15 March 2019
First version publication date	15 March 2019

Trial information

Trial identification

Sponsor protocol code	ADS-AMT-PD302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02202551
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Adamas Pharmaceuticals, Inc.
Sponsor organisation address	1900 Powell Street, Suite 1000, Emeryville,, California, United States, 94608
Public contact	Dorothy Engelking, Adamas Pharmaceuticals, Inc., 510 4503551, dengelking@adamaspharma.com
Scientific contact	Dorothy Engelking, Adamas Pharmaceuticals, Inc., 510 4503551, dengelking@adamaspharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2018
Global end of trial reached?	Yes
Global end of trial date	28 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of ADS-5102 oral capsules, an extended release formulation of amantadine, administered at a dose of 340 mg once nightly at bedtime for the treatment of levodopa induced dyskinesia (LID) in subjects with Parkinson's disease (PD).

Protection of trial subjects:

This study was conducted in compliance with Good Clinical Practice (GCP) according to the United States (US) Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRB, REB, or IEC (21 CFR 56), the obligations of clinical investigators (21 CFR 312), International Conference for Harmonisation GCP guidelines, and with the ethical principles originating in the Declaration of Helsinki.

Written informed consent was obtained from all study subjects before any study-related procedures were performed. The investigator or designee fully explained, in layman’s terms, the nature of the study, along with the aims, methods, potential risks, and any discomfort that participation may entail, as well as insurance and other procedures for compensation in case of injury. The investigator explained that the study was for research purposes only and that therapeutic benefit to the subject may not have been an outcome of participation. The investigator also explained that subjects were completely free to refuse to enter the study or to withdraw from it at any time without prejudice. Each subject acknowledged receipt of this information by giving written informed consent (i.e., signing the ICF) for participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	United States: 152
Worldwide total number of subjects	223
EEA total number of subjects	71

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)	109
From 65 to 84 years	114
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	223
Number of subjects completed	223

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1A

Arm description:

Subjects who completed an Adamas efficacy study evaluating ADS-5102 in LID (and received ADS-5102) and chose to immediately transition into the current study without a time gap.

Arm type	Experimental
Investigational medicinal product name	ADS-5102 capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received a daily ADS-5102 dose of 170 mg (1 ADS-5102-containing capsule) during the first week of treatment, 340 mg (2 ADS-5102 capsules) during Weeks 2 through 100, and 170 mg (1 ADS-5102 capsule) during the last week of treatment. Study drug was to be taken once daily at bedtime (if possible, no earlier than 9 pm). Capsules were to be swallowed intact, and were to be taken with any nonalcoholic beverage, with or without food.

Arm title	Group 1P

Arm description:

Subjects who completed an Adamas efficacy study evaluating ADS-5102 in LID (and received placebo) and chose to immediately transition into the current study without a time gap.

Arm type	Experimental
Investigational medicinal product name	ADS-5102 capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received a daily ADS-5102 dose of 170 mg (1 ADS-5102-containing capsule) during the first week of treatment, 340 mg (2 ADS-5102 capsules) during Weeks 2 through 100, and 170 mg (1 ADS-5102 capsule) during the last week of treatment. Study drug was to be taken once daily at bedtime (if possible, no earlier than 9 pm). Capsules were to be swallowed intact, and were to be taken with any nonalcoholic beverage, with or without food.

Arm title	Group 2

Arm description:

Subjects who completed a previous Adamas efficacy study evaluating ADS-5102 in LID and entered the current study with a time gap

Arm type	Experimental
Investigational medicinal product name	ADS-5102 capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received a daily ADS-5102 dose of 170 mg (1 ADS-5102-containing capsule) during the first week of treatment, 340 mg (2 ADS-5102 capsules) during Weeks 2 through 100, and 170 mg (1 ADS-5102 capsule) during the last week of treatment. Study drug was to be taken once daily at bedtime (if possible, no earlier than 9 pm). Capsules were to be swallowed intact, and were to be taken with any nonalcoholic beverage, with or without food.

Arm title	Group 3

Arm description:

Subjects who would have been deemed ineligible for participation in a previous Adamas efficacy study due to having undergone deep brain stimulation (DBS).

Arm type	Experimental
Investigational medicinal product name	ADS-5102 capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received a daily ADS-5102 dose of 170 mg (1 ADS-5102-containing capsule) during the first week of treatment, 340 mg (2 ADS-5102 capsules) during Weeks 2 through 100, and 170 mg (1 ADS-5102 capsule) during the last week of treatment. Study drug was to be taken once daily at bedtime (if possible, no earlier than 9 pm). Capsules were to be swallowed intact, and were to be taken with any nonalcoholic beverage, with or without food.

Number of subjects in period 1	Group 1A	Group 1P	Group 2
Started	60	78	24
Completed	35	41	14
Not completed	25	37	10
Subject unwilling to proceed	1	6	2
Sponsor's decision	3	-	-
Consent withdrawn by subject	-	3	1
Other	11	8	3
Lost to follow-up	-	1	1

Subject discontinued study drug	10	19	3

Number of subjects in period 1	Group 3
Started	61
Completed	39
Not completed	22
Subject unwilling to proceed	4
Sponsor's decision	-
Consent withdrawn by subject	2
Other	5
Lost to follow-up	1
Subject discontinued study drug	10

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	223	223	
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)	109	109	
From 65-84 years	114	114	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	63.7		
standard deviation	± 9.32	-	
Gender categorical Units: Subjects			
Female	92	92	
Male	131	131	

End points

End points reporting groups

Reporting group title	Group 1A
Reporting group description:	
Subjects who completed an Adamas efficacy study evaluating ADS-5102 in LID (and received ADS-5102) and chose to immediately transition into the current study without a time gap.	
Reporting group title	Group 1P
Reporting group description:	
Subjects who completed an Adamas efficacy study evaluating ADS-5102 in LID (and received placebo) and chose to immediately transition into the current study without a time gap.	
Reporting group title	Group 2
Reporting group description:	
Subjects who completed a previous Adamas efficacy study evaluating ADS-5102 in LID and entered the current study with a time gap	
Reporting group title	Group 3
Reporting group description:	
Subjects who would have been deemed ineligible for participation in a previous Adamas efficacy study due to having undergone deep brain stimulation (DBS).	

Primary: Adverse events

End point title	Adverse events[1]
End point description:	
End point type	Primary
End point timeframe:	
From start of dosing to end of study.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per protocol there were no statistical analyses conducted for this end point.

End point values	Group 1A	Group 1P	Group 2	Group 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	78	24	61
Units: Subjects				
Adverse Events	57	70	23	55
Study drug-related adverse events	31	45	16	32
Serious adverse events	16	21	6	17
Study drug-related serious adverse events	1	3	0	1
Permanently discontinued IMP due to AE	12	21	6	10
Permanently discontinued IMP due to related AE	4	15	4	8

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From start of dosing to end of study.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Group 1A
Reporting group description: Subjects who completed an Adamas efficacy study evaluating ADS-5102 in LID (and received ADS-5102) and chose to immediately transition into the current study without a time gap.	
Reporting group title	Group 1P
Reporting group description: Subjects who completed an Adamas efficacy study evaluating ADS-5102 in LID (and received placebo) and chose to immediately transition into the current study without a time gap.	
Reporting group title	Group 2
Reporting group description: Subjects who completed a previous Adamas efficacy study evaluating ADS-5102 in LID and entered the current study with a time gap	
Reporting group title	Group 3
Reporting group description: Subjects who would have been deemed ineligible for participation in a previous Adamas efficacy study due to having undergone deep brain stimulation (DBS).	

Serious adverse events	Group 1A	Group 1P	Group 2
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 60 (26.67%)	21 / 78 (26.92%)	6 / 24 (25.00%)
number of deaths (all causes)	4	2	2
number of deaths resulting from adverse events	4	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (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

Venous thrombosis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (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			
Adverse drug reaction			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Abasia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory arrest			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Haemothorax			

subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Respiratory distress			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
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			
Psychotic disorder			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 60 (1.67%)	1 / 78 (1.28%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Mental status changes			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (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
Suicidal ideation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (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
Mania			

subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Radius fracture			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Joint dislocation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Hip fracture			
subjects affected / exposed	1 / 60 (1.67%)	2 / 78 (2.56%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Femur fracture			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Traumatic fracture			

subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Acetabulum fracture			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Pelvic fracture			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Confusion postoperative			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Wrist fracture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (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
Craniocerebral injury			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (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
Forearm fracture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (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			
Acute myocardial infarction			

subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Cardiac arrest			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Myocardial infarction			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Hypertensive cardiomyopathy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			

subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Neuroleptic malignant syndrome			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Parkinson's disease			
subjects affected / exposed	1 / 60 (1.67%)	1 / 78 (1.28%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
On and off phenomenon			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Restless legs syndrome			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Hypokinesia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (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
Intercostal neuralgia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyskinesia			

subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Volvulus			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Colonic pseudo-obstruction			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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	1 / 60 (1.67%)	1 / 78 (1.28%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 60 (1.67%)	1 / 78 (1.28%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain upper			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Arthritis bacterial			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Osteoarthritis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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
Rhabdomyolysis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Arthralgia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	0 / 24 (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			
Clostridium difficile sepsis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (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

Septic shock			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	0 / 24 (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
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Staphylococcus sepsis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
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	Group 3		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 61 (27.87%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abasia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			

Benign prostatic hyperplasia				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Respiratory arrest				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Psychotic disorder				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Anxiety				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mania				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Laceration				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Ankle fracture				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic fracture				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acetabulum fracture				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Confusion postoperative				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Craniocerebral injury				

subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Forearm fracture				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				

subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertensive cardiomyopathy				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Encephalopathy				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuroleptic malignant syndrome				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Parkinson's disease				
subjects affected / exposed	3 / 61 (4.92%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
On and off phenomenon				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Restless legs syndrome				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokinesia				

subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intercostal neuralgia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyskinesia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Volvulus			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colonic pseudo-obstruction			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Constipation				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteonecrosis				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rhabdomyolysis				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arthralgia				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Joint effusion			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Clostridium difficile sepsis			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pseudomonal sepsis			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Staphylococcus sepsis			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group 1A	Group 1P	Group 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 60 (95.00%)	70 / 78 (89.74%)	23 / 24 (95.83%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 60 (0.00%)	4 / 78 (5.13%)	1 / 24 (4.17%)
occurrences (all)	0	4	1
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 60 (3.33%)	6 / 78 (7.69%)	0 / 24 (0.00%)
occurrences (all)	2	6	0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	10 / 60 (16.67%)	12 / 78 (15.38%)	2 / 24 (8.33%)
occurrences (all)	10	12	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 60 (5.00%)	2 / 78 (2.56%)	2 / 24 (8.33%)
occurrences (all)	3	2	2
Psychiatric disorders			
Hallucination (pooled)	Additional description: The Hallucinations (Pooled) term combines all Preferred Terms that contain the term "Hallucination".		
subjects affected / exposed	15 / 60 (25.00%)	24 / 78 (30.77%)	5 / 24 (20.83%)
occurrences (all)	15	24	5
Hallucination, visual			
subjects affected / exposed	14 / 60 (23.33%)	24 / 78 (30.77%)	4 / 24 (16.67%)
occurrences (all)	14	24	4
Insomnia			
subjects affected / exposed	8 / 60 (13.33%)	5 / 78 (6.41%)	4 / 24 (16.67%)
occurrences (all)	8	5	4

Depression			
subjects affected / exposed	4 / 60 (6.67%)	5 / 78 (6.41%)	2 / 24 (8.33%)
occurrences (all)	4	5	2
Anxiety			
subjects affected / exposed	3 / 60 (5.00%)	6 / 78 (7.69%)	1 / 24 (4.17%)
occurrences (all)	3	6	1
Abnormal dreams			
subjects affected / exposed	5 / 60 (8.33%)	4 / 78 (5.13%)	2 / 24 (8.33%)
occurrences (all)	5	4	2
Rapid eye movements sleep abnormal			
subjects affected / exposed	1 / 60 (1.67%)	4 / 78 (5.13%)	3 / 24 (12.50%)
occurrences (all)	1	4	3
Confusional state			
subjects affected / exposed	2 / 60 (3.33%)	3 / 78 (3.85%)	3 / 24 (12.50%)
occurrences (all)	2	3	3
Sleep disorder			
subjects affected / exposed	1 / 60 (1.67%)	6 / 78 (7.69%)	0 / 24 (0.00%)
occurrences (all)	1	6	0
Investigations			
Weight decreased			
subjects affected / exposed	4 / 60 (6.67%)	4 / 78 (5.13%)	0 / 24 (0.00%)
occurrences (all)	4	4	0
Glomerular filtration rate decreased			
subjects affected / exposed	2 / 60 (3.33%)	4 / 78 (5.13%)	0 / 24 (0.00%)
occurrences (all)	2	4	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	13 / 60 (21.67%)	29 / 78 (37.18%)	8 / 24 (33.33%)
occurrences (all)	13	29	8
Contusion			
subjects affected / exposed	4 / 60 (6.67%)	2 / 78 (2.56%)	0 / 24 (0.00%)
occurrences (all)	4	2	0
Laceration			
subjects affected / exposed	3 / 60 (5.00%)	1 / 78 (1.28%)	0 / 24 (0.00%)
occurrences (all)	3	1	0
Wrist fracture			

subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Head injury			
subjects affected / exposed	3 / 60 (5.00%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences (all)	3	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 60 (6.67%)	10 / 78 (12.82%)	5 / 24 (20.83%)
occurrences (all)	4	10	5
On and off phenomenon			
subjects affected / exposed	7 / 60 (11.67%)	4 / 78 (5.13%)	4 / 24 (16.67%)
occurrences (all)	7	4	4
Parkinson's disease			
subjects affected / exposed	3 / 60 (5.00%)	5 / 78 (6.41%)	1 / 24 (4.17%)
occurrences (all)	3	5	1
Cognitive disorder			
subjects affected / exposed	2 / 60 (3.33%)	2 / 78 (2.56%)	3 / 24 (12.50%)
occurrences (all)	2	2	3
Balance disorder			
subjects affected / exposed	0 / 60 (0.00%)	2 / 78 (2.56%)	3 / 24 (12.50%)
occurrences (all)	0	2	3
Syncope			
subjects affected / exposed	3 / 60 (5.00%)	1 / 78 (1.28%)	1 / 24 (4.17%)
occurrences (all)	3	1	1
Headache			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	2
Somnolence			
subjects affected / exposed	0 / 60 (0.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Eye disorders			
Cataract			
subjects affected / exposed	3 / 60 (5.00%)	1 / 78 (1.28%)	1 / 24 (4.17%)
occurrences (all)	3	1	1
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	9 / 60 (15.00%)	12 / 78 (15.38%)	6 / 24 (25.00%)
occurrences (all)	9	12	6
Nausea			
subjects affected / exposed	7 / 60 (11.67%)	8 / 78 (10.26%)	6 / 24 (25.00%)
occurrences (all)	7	8	6
Dry mouth			
subjects affected / exposed	4 / 60 (6.67%)	6 / 78 (7.69%)	4 / 24 (16.67%)
occurrences (all)	4	6	4
Vomiting			
subjects affected / exposed	1 / 60 (1.67%)	2 / 78 (2.56%)	3 / 24 (12.50%)
occurrences (all)	1	2	3
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 60 (5.00%)	0 / 78 (0.00%)	2 / 24 (8.33%)
occurrences (all)	3	0	2
Abdominal pain			
subjects affected / exposed	3 / 60 (5.00%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences (all)	3	0	0
Skin and subcutaneous tissue disorders			
Livedo reticularis			
subjects affected / exposed	6 / 60 (10.00%)	5 / 78 (6.41%)	3 / 24 (12.50%)
occurrences (all)	6	5	3
Dry skin			
subjects affected / exposed	0 / 60 (0.00%)	1 / 78 (1.28%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 60 (3.33%)	4 / 78 (5.13%)	1 / 24 (4.17%)
occurrences (all)	2	4	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 60 (6.67%)	5 / 78 (6.41%)	2 / 24 (8.33%)
occurrences (all)	4	5	2
Arthralgia			
subjects affected / exposed	5 / 60 (8.33%)	5 / 78 (6.41%)	1 / 24 (4.17%)
occurrences (all)	5	5	1

Pain in extremity			
subjects affected / exposed	4 / 60 (6.67%)	1 / 78 (1.28%)	1 / 24 (4.17%)
occurrences (all)	4	1	1
Osteoarthritis			
subjects affected / exposed	3 / 60 (5.00%)	1 / 78 (1.28%)	0 / 24 (0.00%)
occurrences (all)	3	1	0
Muscle spasms			
subjects affected / exposed	1 / 60 (1.67%)	0 / 78 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	7 / 60 (11.67%)	8 / 78 (10.26%)	3 / 24 (12.50%)
occurrences (all)	7	8	3
Nasopharyngitis			
subjects affected / exposed	4 / 60 (6.67%)	4 / 78 (5.13%)	1 / 24 (4.17%)
occurrences (all)	4	4	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 60 (6.67%)	3 / 78 (3.85%)	3 / 24 (12.50%)
occurrences (all)	4	3	3
Cellulitis			
subjects affected / exposed	3 / 60 (5.00%)	0 / 78 (0.00%)	2 / 24 (8.33%)
occurrences (all)	3	0	2
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)	1 / 78 (1.28%)	2 / 24 (8.33%)
occurrences (all)	1	1	2
Metabolism and nutrition disorders			
Vitamin B12 deficiency			
subjects affected / exposed	3 / 60 (5.00%)	0 / 78 (0.00%)	1 / 24 (4.17%)
occurrences (all)	3	0	1
Vitamin D deficiency			
subjects affected / exposed	3 / 60 (5.00%)	0 / 78 (0.00%)	0 / 24 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	Group 3		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 61 (90.16%)		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	12 / 61 (19.67%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Psychiatric disorders			
Hallucination (pooled)	Additional description: The Hallucinations (Pooled) term combines all Preferred Terms that contain the term "Hallucination".		
subjects affected / exposed	10 / 61 (16.39%)		
occurrences (all)	10		
Hallucination, visual			
subjects affected / exposed	10 / 61 (16.39%)		
occurrences (all)	10		
Insomnia			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
Depression			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
Anxiety			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
Abnormal dreams			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
Rapid eye movements sleep			

abnormal			
subjects affected / exposed	3 / 61 (4.92%)		
occurrences (all)	3		
Confusional state			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences (all)	0		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	23 / 61 (37.70%)		
occurrences (all)	23		
Contusion			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences (all)	0		
Wrist fracture			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences (all)	0		
Head injury			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 61 (4.92%)		
occurrences (all)	3		

On and off phenomenon subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3		
Parkinson's disease subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 6		
Cognitive disorder subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0		
Balance disorder subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Syncope subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Headache subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Somnolence subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Eye disorders Cataract subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3		
Nausea subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Dry mouth subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3		
Vomiting			

subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2		
Abdominal pain subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Livedo reticularis subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 6		
Dry skin subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Renal and urinary disorders			
Urinary retention subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0		
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Arthralgia subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Pain in extremity subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Osteoarthritis subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3		
Muscle spasms subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Infections and infestations			

Urinary tract infection subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 5		
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2		
Cellulitis subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0		
Pneumonia subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0		
Metabolism and nutrition disorders Vitamin B12 deficiency subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2014	Amendment 1 included the following key changes: • Increased the total number of subjects planned from 150 to 200 • Increased the number of study sites from approximately 45 to 55 to 80 and broadened the potential regions from the US and Canada to worldwide • Changed the efficacy measure from the Unified Dyskinesia Rating Scale (UDysRS) to the MDS-UPDRS. (Note: A total of 9 subjects provided UDysRS data prior to Amendment 1; all 9 subjects provided data at Screening, and 4 of these subjects provided data at Week 4. The UDysRS data from these subjects are not included in the database and are not discussed in this clinical study report.) • Allowed entry of subjects who had undergone DBS • Broadened entry criteria to allow subjects from any ADS-5102 LID efficacy study, rather than just ADS-AMT-PD301 • Categorized subjects entering the study into 3 groups, for clarity • Removed the need to keep concomitant medications stable while on study • Removed a washout period for prior amantadine use • For subjects in Group 3, removed the exclusion of lack of response to prior amantadine
07 October 2014	Amendment 2 included the following key changes: • Added US IND number and EudraCT number • Clarified that the end of the study was when the last subject completed the last visit • For subjects in Group 3, modified exclusion criterion regarding cancer from "history of cancer since completion of participation in previous Adamas trial" to "history of cancer within 5 years of Screening" • Added statement that labeling of study drug would be compliant with European Union guidelines • Added that dosing details of an overdose of study drug or a concomitant medication were to be recorded on the appropriate eCRF(s) • Added definition of a suspected unexpected serious adverse reaction • Clarified definition of an unexpected SAE • Updated AE reporting requirements to include Eudravigilance • Updated language regarding subject confidentiality and ethical conduct of the study
07 January 2015	Amendment 3 included the following key changes: • Revised exclusion criterion regarding sexually active females to specify that a highly effective hormonal method of contraception was to be used in combination with a barrier method (Groups 1, 2, and 3) • Added that subjects with untreated angle closure glaucoma would be excluded (Groups 2 and 3) • Added that subjects with suicidal ideation, history of suicidal ideation, or suicide attempt during prior amantadine use would be excluded (Groups 2 and 3) • Added that subjects were not eligible for study participation if they were taking a medication that could prolong the QT interval and had a known risk of torsades de pointes; to be eligible for the study, the medication had to have been stopped 60 days prior to Screening. Added a list of these types of medications to an appendix • Added a urine pregnancy test at Week 4, 8, 16, 28, 40, and 52

16 July 2015	Amendment 4 included the following key changes: • Increased the number of subjects (up to 250) and increased the number of study sites (to approximately 90) • Increased the treatment duration to 101 weeks. Added clinical visits and modified procedures and assessments to accommodate this longer treatment duration • Clarified that male or female subjects, 35 to 85 years of age, inclusive, were eligible for study participation (Group 3) • Deleted a reference to use of the mixed model for repeated measures statistical method, which are not appropriate for this open label study. • Clarified that observed data would be reported and that missing data would not be imputed. Note: although this statement was added to the protocol amendment, the statistical analysis plan included imputation rules for missing efficacy data as well as for missing dates of prior medications and AEs, and missing AE causality.

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.

For non-serious adverse events only the number of subjects experiencing each event were reported, not number of occurrences. Therefore the number of occurrences is entered as the number of subjects experiencing the event.

Notes: