Clinical trial results:
A 12-WEEK, MULTICENTER, RANDOMIZED, PARALLEL-GROUP STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS, BIOMARKER EFFECTS, EFFICACY, AND EFFECT ON MICROGLIA ACTIVATION, AS MEASURED BY POSITRON EMISSION TOMOGRAPHY, OF AZD3241 IN SUBJECTS WITH MULTIPLE SYSTEM ATROPHY

Summary

EudraCT number	2014-004902-13
Trial protocol	GB FI SE
Global end of trial date	29 September 2016

Results information

Result version number	v1 (current)
This version publication date	20 August 2017
First version publication date	20 August 2017

Trial information

Trial identification

Sponsor protocol code	D0490C00023

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Pepparedsleden 1, Molndal, Sweden, SE - 431 83
Public contact	AstraZeneca AB, AstraZeneca AB, Clinicaltrialtransparency@astrazeneca.net
Scientific contact	AstraZeneca AB, AstraZeneca AB, Clinicaltrialtransparency@astrazeneca.net

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	26 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2016
Global end of trial reached?	Yes
Global end of trial date	29 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study were:
• To assess the safety and tolerability of AZD3241 in subjects with MSA.
• To determine the effect of AZD3241 on microglia activation, as measured by [11C]PBR28 binding, in subjects with MSA.

Protection of trial subjects:

Periodic review of patient safety (quarterly review)
Interim analysis when 40 subjects had reached 4 weeks of treatment with potential to stop a treatment arm for patient safety. Conducted in April 2016, with recommendation to continue per protocol.

Background therapy:

Allowed if stable for minimum of 30 days dosing and not on list of prohibited medications.

Evidence for comparator:

Placebo used since currently no specific treatments for Multiple System Atropy.

Actual start date of recruitment	22 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	59
EEA total number of subjects	35

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)	45
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

124 subjects were screened,signed consent. A total of 59 subjects were dispensed treatment through randomization. 1 subject was notified as ineligible prior to first dose, provided no safety data and is excluded from analysis data sets.

Pre-assignment

Screening details:

Rescreening was permitted if eligibility could not be confirmed within the 49 day screening period.
A total of 59 were actually considered to have completed screening and were randomized, 58 were included in analyses as 1 subject not dosed provided no information.

Period 1

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

Blinding implementation details:

subjects assigned treatment through central randomisation schedule

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo to match AZD3241 dosed twice daily

Arm type	Placebo
Investigational medicinal product name	Placebo (to match AZD3241)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0 mg, Twice daily, Week 1

Arm title	AZD3241 300 mg

Arm description:

AZD3241 300 mg dosed twice daily

Arm type	Experimental
Investigational medicinal product name	AZD3241 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg, Twice daily, Week 1

Arm title	AZD3241 600 mg

Arm description:

AZD3241 600 mg dosed twice daily

Arm type	Experimental

Investigational medicinal product name	AZD3241 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg, Twice daily, Week 1

Number of subjects in period 1[1]	Placebo	AZD3241 300 mg	AZD3241 600 mg
Started	19	19	20
Completed	17	16	18
Not completed	2	3	2
Determined not eligible	1	1	1
Adverse event, non-fatal	1	2	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 61 subjects were issued randomization assignments, 2 were determined to be screen failures and were never dispensed study medication, thus 59 were dispensed study medication. 1 additional subject (randomized to placebo group) was determined to be a screen failure after the subject left the study site, and was notified by the site prior to the first dose. The subject refused to return to the site, and provided no safety information. Thus only 58 subjects were included in the Safety analysis se

Period 2

Period 2 title	Dose escalation Week 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

continuation of study

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo to match AZD3241 dosed twice daily

Arm type	Placebo
Investigational medicinal product name	Placebo (to match AZD3241)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0 mg, Twice daily, Week 2

Arm title	AZD3241 300 mg

Arm description: AZD3241 300 mg dosed twice daily	
Arm type	Experimental
Investigational medicinal product name	AZD3241 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 300 mg, Twice daily, Week 2	
Arm title	AZD3241 600 mg
Arm description: AZD3241 600 mg dosed twice daily	
Arm type	Experimental
Investigational medicinal product name	AZD3241 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 300 mg, Twice daily, Week 2	

Number of subjects in period 2	Placebo	AZD3241 300 mg	AZD3241 600 mg
Started	17	16	18
Completed	16	14	17
Not completed	1	2	1
Determined not eligible	1	1	

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Arm title	Placebo
Arm description: Placebo to match AZD3241 dosed twice daily	
Arm type	Placebo
Investigational medicinal product name	Plcebo to match AZD3241
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 0 mg, Twice a day, Week 3 through 12	
Arm title	AZD3241 300 mg
Arm description: AZD3241 300 mg dosed twice daily	
Arm type	Experimental
Investigational medicinal product name	AZD3241 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 300 mg, Twice daily, Week 3 through 12	
Arm title	AZD3241 600 mg
Arm description: AZD3241 600 mg dosed twice daily	
Arm type	Experimental
Investigational medicinal product name	AZD3241 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Two 300 mg, Twice daily, Week 3 through 12	

Number of subjects in period 3	Placebo	AZD3241 300 mg	AZD3241 600 mg
Started	16	14	17
Completed	15	13	17
Not completed	1	1	0
Adverse event, non-fatal	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo to match AZD3241 dosed twice daily	
Reporting group title	AZD3241 300 mg
Reporting group description: AZD3241 300 mg dosed twice daily	
Reporting group title	AZD3241 600 mg
Reporting group description: AZD3241 600 mg dosed twice daily	

Reporting group values	Placebo	AZD3241 300 mg	AZD3241 600 mg
Number of subjects	19	19	20
Age categorical Units: Subjects			
Adults (18-64 years)	14	15	15
From 65-84 years	5	4	5
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	59.3	59.9	58
standard deviation	± 7.9	± 6.1	± 8.5
Gender, Male/Female Units: Subjects			
Female	7	5	5
Male	12	14	15
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	0
White	16	15	16
More than one race	0	0	0
Unknown or Not Reported	2	3	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	16	16	18
Unknown or Not Reported	2	3	2
Multiple System Atropy Subtype			
Multiple System Atropy (MSA) Subtype, Parkinsonian (P) or Cerebellar (C)			
Units: Subjects			
MSA - P	7	10	7
MSA - C	12	9	13
Diagnostic Category			

Diagnostic Category for Multiple System Atropy (MSA); Possible or Probable were the eligible categories			
Units: Subjects			
Possible MSA	1	4	8
Probable MSA	18	15	12
Genotype			
Translocator Protein binding (TSPO) : genotype (affinity for binding); Low Affinity Binding was exclusionary			
Units: Subjects			
TSPO - High Affinity Binding	12	10	16
TSPO - Mixed Affinity Binding	7	9	4
TSPO- Low Affinity Binding	0	0	0

Reporting group values	Total		
Number of subjects	58		
Age categorical Units: Subjects			
Adults (18-64 years)	44		
From 65-84 years	14		
85 years and over	0		
Age Continuous Units: Years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	17		
Male	41		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	3		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	47		
More than one race	0		
Unknown or Not Reported	7		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	50		
Unknown or Not Reported	7		
Multiple System Atropy Subtype			
Multiple System Atropy (MSA) Subtype, Parkinsonian (P) or Cerebellar (C)			
Units: Subjects			
MSA - P	24		
MSA - C	34		
Diagnostic Category			
Diagnostic Category for Multiple System Atropy (MSA); Possible or Probable were the eligible categories			
Units: Subjects			
Possible MSA	13		
Probable MSA	45		

Genotype			
Translocator Protein binding (TSPO) : genotype (affinity for binding); Low Affinity Binding was exclusionary			
Units: Subjects			
TSPO - High Affinity Binding	38		
TSPO - Mixed Affinity Binding	20		
TSPO- Low Affinity Binding	0		

Subject analysis sets

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects randomised who took at least one dose of study medication (1 subject in the Placebo, not included, withdrawn before first dose)

Subject analysis set title	PET Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects with PET scan at baseline and at week 12

Reporting group values	Safety Analysis Set	PET Analysis Set	
Number of subjects	58	43	
Age categorical Units: Subjects			
Adults (18-64 years)	44	33	
From 65-84 years	14	10	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	59	60.5	
standard deviation	± 7.5	± 7.8	
Gender, Male/Female Units: Subjects			
Female	17	13	
Male	41	30	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	3	2	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	0	
White	47	36	
More than one race	0	0	
Unknown or Not Reported	7	5	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	50	37	
Unknown or Not Reported	7	5	
Multiple System Atropy Subtype			
Multiple System Atropy (MSA) Subtype, Parkinsonian (P) or Cerebellar (C)			

Units: Subjects			
MSA - P	34	26	
MSA - C	24	17	
Diagnostic Category			
Diagnostic Category for Multiple System Atropy (MSA); Possible or Probable were the eligible categories			
Units: Subjects			
Possible MSA	13	8	
Probable MSA	45	35	
Genotype			
Translocator Protein binding (TSPO) : genotype (affinity for binding); Low Affinity Binding was exclusionary			
Units: Subjects			
TSPO - High Affinity Binding	38	29	
TSPO - Mixed Affinity Binding	20	14	
TSPO- Low Affinity Binding	0	0	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo to match AZD3241 dosed twice daily	
Reporting group title	AZD3241 300 mg
Reporting group description: AZD3241 300 mg dosed twice daily	
Reporting group title	AZD3241 600 mg
Reporting group description: AZD3241 600 mg dosed twice daily	
Reporting group title	Placebo
Reporting group description: Placebo to match AZD3241 dosed twice daily	
Reporting group title	AZD3241 300 mg
Reporting group description: AZD3241 300 mg dosed twice daily	
Reporting group title	AZD3241 600 mg
Reporting group description: AZD3241 600 mg dosed twice daily	
Reporting group title	Placebo
Reporting group description: Placebo to match AZD3241 dosed twice daily	
Reporting group title	AZD3241 300 mg
Reporting group description: AZD3241 300 mg dosed twice daily	
Reporting group title	AZD3241 600 mg
Reporting group description: AZD3241 600 mg dosed twice daily	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects randomised who took at least one dose of study medication (1 subject in the Placebo, not included, withdrawn before first dose)	
Subject analysis set title	PET Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description: Subjects with PET scan at baseline and at week 12	

Primary: Striatum Brain region: Change from baseline in microglia activation via Positron Emission Tomography(PET)

End point title	Striatum Brain region: Change from baseline in microglia activation via Positron Emission Tomography(PET)
End point description: Striatum Brain region: Change from baseline in microglia activation via PET By [11C]PBR28 binding to translocator protein (looking for decrease in total distribution volume)	
End point type	Primary
End point timeframe: Baseline (pre randomization) and Week 12	

End point values	Placebo	AZD3241 300 mg	AZD3241 600 mg	PET Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	16	14	17	43
Units: Total distribution Volume (VT)				
arithmetic mean (standard deviation)	-0.26 (± 0.75)	-0.08 (± 0.84)	-0.31 (± 1.37)	-0.25 (± 1.09)

Statistical analyses

Statistical analysis title	Placebo change from baseline
Statistical analysis description: Change from baseline within treatment arm compared to 0	
Comparison groups	Placebo v PET Analysis Set
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.13 [1]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.38
Confidence interval	
level	90 %
sides	1-sided
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:
[1] - Not adjusted for multiple comparisons, alpha=0.10

Statistical analysis title	AZD3241 300 mg change from baseline
Statistical analysis description: Change from baseline within treatment compared to 0	
Comparison groups	AZD3241 300 mg v PET Analysis Set
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.91 [2]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	90 %
sides	1-sided
upper limit	0.4

Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:
[2] - not adjusted

Statistical analysis title	AZD3241 600 mg change from baseline
Statistical analysis description: Change from baseline within treatment compared to 0	
Comparison groups	AZD3241 600 mg v PET Analysis Set
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.68
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	90 %
sides	1-sided
upper limit	0.31
Variability estimate	Standard error of the mean
Dispersion value	0.25

Statistical analysis title	AZD3241 300 mg compared to Placebo
Statistical analysis description: Secondary objective - comparison to placebo	
Comparison groups	Placebo v AZD3241 300 mg v PET Analysis Set
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32 [3]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.35
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.24
upper limit	1.02
Variability estimate	Standard error of the mean
Dispersion value	0.34

Notes:
[3] - no adjustment

Statistical analysis title	AZD3241 600 mg comparison to Placebo
Statistical analysis description: Secondary objective - comparison to placebo	
Comparison groups	Placebo v AZD3241 600 mg v PET Analysis Set

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45 [4]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.28
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.39
upper limit	0.92
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[4] - no adjustment

Secondary: Myeloperoxidase (MPO) inhibition in plasma (change from baseline), specific activity

End point title	Myeloperoxidase (MPO) inhibition in plasma (change from baseline), specific activity

End point description:

Myeloperoxidase (MPO) inhibition in plasma (change from baseline), on samples collected and analyzed, specific activity (activity/protein)

End point type	Secondary

End point timeframe:

Baseline (Day -1) and week 12

End point values	Placebo	AZD3241 300 mg	AZD3241 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	9	15	
Units: ratio				
arithmetic mean (standard deviation)				
Pre dose (week 12)	-0.05 (± 0.15)	-0.12 (± 0.11)	-0.1 (± 0.2)	
1 hour post dose (week 12)	0.08 (± 0.28)	-0.18 (± 0.24)	0.19 (± 1.3)	
2 to 6 hours post dose (week 12)	0.03 (± 0.23)	-0.19 (± 0.24)	-0.15 (± 0.14)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Exploratory efficacy: Unified Multiple System Atropy Rating Scale, change from baseline (Total Score, Part 1 + Part 2)

End point title	Exploratory efficacy: Unified Multiple System Atropy Rating Scale, change from baseline (Total Score, Part 1 + Part 2)

End point description:	
Exploratory efficacy: Unified Multiple System Atropy Rating Scale, change from baseline (total Score, Part 1 + Part 2) : Score range 0 to 104, positive value indicates worsening symptoms	
End point type	Other pre-specified
End point timeframe:	
Baseline to final treatment visit (early termination visit for those not completing week 12)	

End point values	Placebo	AZD3241 300 mg	AZD3241 600 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	18	
Units: Score				
arithmetic mean (standard deviation)	4.59 (± 4.46)	3.71 (± 4.98)	2.56 (± 6.15)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
12 weeks of randomized treation plus a follow up period up to 14 days after last dose	
Adverse event reporting additional description:	
Adverse events starting during screening period Before randomization or starting greater that 14 days after the last dose of study medication are not included in these tabulations.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo to match AZD3241 dosed twice daily	
Reporting group title	AZD3241 300 mg
Reporting group description:	
AZD3241 300 mg dosed twice daily	
Reporting group title	AZD3241 600 mg
Reporting group description:	
AZD3241 600 mg dosed twice daily	

Serious adverse events	Placebo	AZD3241 300 mg	AZD3241 600 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	1 / 20 (5.00%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (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			
Multipla System Atrophy	Additional description: Subject found face down on bedding - considered disease related death		
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			

Choking	Additional description: Subject found dead with cheese in throat		
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (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

Frequency threshold for reporting non-serious adverse events: 1 %

Alcohol use			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 19 (10.53%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	1
Dyspnoea			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Sleep apnoe syndrome			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Depressive symptom			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Abnormal dreams			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Disorientation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Panic attack			

subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Suicidal ideation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Weight increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Administration related reaction			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	4 / 20 (20.00%)
occurrences (all)	12	1	6
Procedural pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Thermal burn			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
atrial fibrilation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	1	1	0

Clumsiness			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	2 / 19 (10.53%)	2 / 19 (10.53%)	2 / 20 (10.00%)
occurrences (all)	2	2	4
Dysarthria			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	4 / 19 (21.05%)	3 / 19 (15.79%)	2 / 20 (10.00%)
occurrences (all)	5	6	4
Hypokinesia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Lethargy			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Migraine with aura			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	2	3
Radicular pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Restless leg syndrome			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Syncope			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	1	4

Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	2 / 19 (10.53%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	2	1	2
Dysphagia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Salivary hypersecretion			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Nausea			

subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Skin discolouration			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Skin necrosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Joint swelling			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	1 / 20 (5.00%)
occurrences (all)	3	0	1
Muscle fatigue			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Musculoskeletal stiffness			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	1 / 20 (5.00%)
occurrences (all)	0	1	2
Myalgia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Infections and infestations			

Lower respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	4	0
Nasopharyngitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	3 / 19 (15.79%)	5 / 19 (26.32%)	3 / 20 (15.00%)
occurrences (all)	3	5	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2015	Changed designation of Investigational product manufacturer; Updated Reason for discontinuing study drug on study withdrawal (implimented before first patient in)
28 May 2015	Amended options for Data Safety Monitoring Board recommendations based on unblinded interim analysis; Updated prohibitied medication information

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.

Although 59 subjects entered, 1 notified immediately as not eligible, thus only 58 are included in safety analysis set. Biomarker samples included if testing done within 6 months of collection per protocol although during study expiry changed.

Notes: