



Clinical trial results:

A European multicentre double-blind placebo controlled phase III trial of nilvadipine in mild to moderate Alzheimer's disease.

Summary

EudraCT number	2012-002764-27
Trial protocol	GB IE SE HU GR NL IT DE
Global end of trial date	16 December 2016

Results information

Result version number	v1 (current)
This version publication date	30 August 2018
First version publication date	30 August 2018
Summary attachment (see zip file)	NILVAD Clinical Study Report Synopsis (NILVAD synopsis clinical study report.pdf)

Trial information

Trial identification

Sponsor protocol code	NILVAD2012
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02017340
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	St James's Hospital
Sponsor organisation address	James's Street, Dublin, Ireland, Dublin 8
Public contact	Brian Lawlor, St James's Hospital, 353 18968524, lawlorba@tcd.ie
Scientific contact	Brian Lawlor, St James's Hospital, 353 18968524, lawlorba@tcd.ie

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	09 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2016
Global end of trial reached?	Yes
Global end of trial date	16 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of Nilvadipine as a disease course modifying treatment for mild to moderate AD in a phase III double-blind placebo-controlled study.

Protection of trial subjects:

Safety was assessed by physical examination, blood pressure measurements and clinical laboratory tests. Each subject partaking in the study had a blood sample taken for safety purposes, which underwent a series of clinical laboratory tests. Safety blood tests were carried out at the Screening Visit and at Week 78. All subjects had sitting and standing blood pressure (BP) measurements performed at screening, Week 0, Week 6, Week 13, Week 26, Week 39, Week 52, Week 65 and Week 78. The research clinician performed a routine physical examination and neurological examination of each subject at the screening visit. Routine evaluation of general health and wellbeing were conducted at the baseline visit and were repeated at each of the subsequent visits. These and other safety measurements as required were conducted more frequently if clinically indicated or at the discretion of the Investigator. The reason for additional observations was noted in the case report form. Any clinically significant complaints, symptoms, or other abnormalities were followed by appropriate tests and/or procedures until these values returned to normal or to clinically acceptable levels or could be attributed to causes other than the test drug(s). The investigator explained all abnormal findings in the case report form (CRF). All adverse events required reporting. Different reporting procedures were applied for differing types of adverse events. All non serious adverse events events were captured in the AE section of the CRF and sent to the Data Management coordinating centre on a regular basis for entry into the Clinical Database and inclusion in the Annual Safety Reports. All serious adverse events and suspected unexpected serious adverse events were reported to a dedicated email address at the coordinating office in Dublin in an expedited manner. Safety data was reviewed every 6 months by the independent Data Management and Safety Monitoring Board (DMSB).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 April 2013
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: 78
Country: Number of subjects enrolled	Sweden: 21
Country: Number of subjects enrolled	United Kingdom: 65
Country: Number of subjects enrolled	France: 58
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Greece: 100
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Ireland: 111

Country: Number of subjects enrolled	Italy: 55
Worldwide total number of subjects	511
EEA total number of subjects	511

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)	92
From 65 to 84 years	393
85 years and over	26

Subject disposition

Recruitment

Recruitment details:

There were 23 recruiting clinical sites in total with 2 sites in Ireland, 1 in the UK, 7 in France, 4 in Italy, 1 in Hungary, 3 in Greece, 1 in Germany, 1 in Sweden and 3 in the Netherlands. The first subject was enrolled on 15th May 2013 and the last subject last visit was 2nd November 2016.

Pre-assignment

Screening details:

Subjects diagnosed with mild to moderate AD who were suitable for treatment with nilvadipine were screened. Patients were screened within a 6 week period before the baseline evaluation. Clinical laboratory tests were conducted after informed consent was completed to determine eligibility. Once deemed eligible subjects proceeded to a baseline visit.

Pre-assignment period milestones

Number of subjects started	511
Number of subjects completed	498

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	No follow-up assessment: 12

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nilvadipine

Arm description:

The test drug was an over-encapsulated 8 mg slow release nilvadipine taken orally once a day after breakfast.

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

Dosage and administration details:

Oral administration taken once daily after breakfast.

Arm title	Placebo
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Arm description:

Subjects randomised to placebo.

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

Dosage and administration details:

Oral administration taken once daily after breakfast.

Number of subjects in period 1^[1]	Nilvadipine	Placebo
Started	247	251
Completed	247	251

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: 13 participants who were included in the worldwide enrollment figure were excluded from the mITT group. One participant withdrew consent after enrollment and 12 participants were excluded from the mITT group due to not completing follow-up assessments. Please see the subject non-completion reasons described in the pre-assignment period section.

Please note that the mITT groups are defined by the ADAS-Cog endpoint alone, and there were additional subjects who underwent secondary assessments.

Period 2

Period 2 title	Week 13
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Nilvadipine

Arm description:

The test drug was an over-encapsulated 8 mg slow release nilvadipine taken orally once a day after breakfast.

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

Dosage and administration details:

Oral administration taken once daily after breakfast.

Arm title	Placebo
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Arm description:

Subjects randomised to placebo.

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

Dosage and administration details:

Oral administration taken once daily after breakfast.

Number of subjects in period 2	Nilvadipine	Placebo
Started	247	251
Completed	247	249
Not completed	0	2
Consent withdrawn by subject	-	1
Physician decision	-	1

Period 3

Period 3 title	Week 52
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	Nilvadipine
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Arm description:

The test drug was an over-encapsulated 8 mg slow release nilvadipine taken orally once a day after breakfast.

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

Dosage and administration details:

Oral administration taken once daily after breakfast.

Arm title	Placebo
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Arm description:

Subjects randomised to placebo.

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

Dosage and administration details:

Oral administration taken once daily after breakfast.

Number of subjects in period 3	Nilvadipine	Placebo
Started	247	249
Completed	232	235
Not completed	15	14
Consent withdrawn by subject	7	8
Adverse event, non-fatal	5	2
Death	2	3
Lost to follow-up	1	-
Protocol deviation	-	1

Period 4

Period 4 title	Week 78
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Nilvadipine

Arm description:

The test drug was an over-encapsulated 8 mg slow release nilvadipine taken orally once a day after breakfast.

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

Dosage and administration details:

Oral administration taken once daily after breakfast.

Arm title	Placebo
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Arm description:

Subjects randomised to placebo.

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

Dosage and administration details:

Oral administration taken once daily after breakfast.

Number of subjects in period 4	Nilvadipine	Placebo
Started	232	235
Completed	222	225
Not completed	10	10
Consent withdrawn by subject	4	5
Adverse event, non-fatal	4	3
Death	1	1
Lost to follow-up	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	Nilvadipine
Reporting group description: The test drug was an over-encapsulated 8 mg slow release nilvadipine taken orally once a day after breakfast.	
Reporting group title	Placebo
Reporting group description: Subjects randomised to placebo.	

Reporting group values	Nilvadipine	Placebo	Total
Number of subjects	247	251	498
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	73.1	72.8	
standard deviation	± 8.66	± 7.84	-
Gender categorical Units: Subjects			
Female	161	147	308
Male	86	104	190
SMMSE			
Standardised Mini-Mental State Examination (SMMSE) (Standish & Molloy, 1997)			
Units: Subjects			
SMMSE < 20	93	94	187
SMMSE ≥ 20	154	157	311

End points

End points reporting groups

Reporting group title	Nilvadipine
Reporting group description: The test drug was an over-encapsulated 8 mg slow release nilvadipine taken orally once a day after breakfast.	
Reporting group title	Placebo
Reporting group description: Subjects randomised to placebo.	
Reporting group title	Nilvadipine
Reporting group description: The test drug was an over-encapsulated 8 mg slow release nilvadipine taken orally once a day after breakfast.	
Reporting group title	Placebo
Reporting group description: Subjects randomised to placebo.	
Reporting group title	Nilvadipine
Reporting group description: The test drug was an over-encapsulated 8 mg slow release nilvadipine taken orally once a day after breakfast.	
Reporting group title	Placebo
Reporting group description: Subjects randomised to placebo.	
Reporting group title	Nilvadipine
Reporting group description: The test drug was an over-encapsulated 8 mg slow release nilvadipine taken orally once a day after breakfast.	
Reporting group title	Placebo
Reporting group description: Subjects randomised to placebo.	
Reporting group title	Nilvadipine
Reporting group description: The test drug was an over-encapsulated 8 mg slow release nilvadipine taken orally once a day after breakfast.	
Reporting group title	Placebo
Reporting group description: Subjects randomised to placebo.	
Subject analysis set title	Modified intention-to-treat
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: An intention-to-treat analysis set, with the additional criterion that participants must have been successfully assessed both at baseline, and at at least one other period of the trial.	

Primary: ADAS-cog 12

End point title	ADAS-cog 12
End point description:	
End point type	Primary
End point timeframe: Baseline, week 13, week 52 and week 78.	

End point values	Nilvadipine	Placebo	Nilvadipine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	247	251	247	245
Units: Arbitrary				
arithmetic mean (standard deviation)	34.4 (± 10.5)	34.5 (± 10.8)	35.2 (± 11.3)	35.3 (± 11.6)

End point values	Nilvadipine	Placebo	Nilvadipine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	215	225	205	208
Units: Arbitrary				
arithmetic mean (standard deviation)	39.4 (± 13.1)	40.3 (± 13.9)	41.9 (± 14.6)	41.9 (± 14.5)

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
This is the primary analysis result, which if statistically significant ($p < 0.05$) will gate the conduct of secondary endpoints promoted to the status of co-primary end-points.	
Comparison groups	Placebo v Nilvadipine v Placebo v Nilvadipine v Placebo v Nilvadipine v Placebo v Nilvadipine
Number of subjects included in analysis	1843
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.465
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Date of first subject enrollment (05th May 2013) to last patient last visit (02nd November 2016).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Nilvadipine
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Nilvadipine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 252 (19.44%)	42 / 257 (16.34%)	
number of deaths (all causes)	3	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign anorectal neoplasm			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone cancer			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Polyp			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interventional procedure			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transurethral bladder resection			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropsychiatric symptoms			
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Injury			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	7 / 252 (2.78%)	5 / 257 (1.95%)	
occurrences causally related to treatment / all	1 / 7	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorder			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Coronary artery disease			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Syncope			
subjects affected / exposed	4 / 252 (1.59%)	3 / 257 (1.17%)	
occurrences causally related to treatment / all	4 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal behaviour			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphonia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cognitive disorder			

subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngo-oesophageal diverticulum			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent placement			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transurethral bladder resection			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transurethral prostatectomy			

subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Femur fracture			
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 252 (1.19%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lymphadenitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	2 / 252 (0.79%)	2 / 257 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	4 / 252 (1.59%)	2 / 257 (0.78%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Nilvadipine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	206 / 252 (81.75%)	201 / 257 (78.21%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Basal cell carcinoma			
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)	
occurrences (all)	0	2	
Benign anorectal neoplasm			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Benign breast neoplasm			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Bladder cancer			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Bladder neoplasm			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Bone cancer			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Colon adenoma			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Melanocytic naevus			

subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Metastasis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Neoplasm progression			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Neoplasm swelling			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Skin cancer			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Skin papilloma			
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences (all)	2	0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Ureteral neoplasm			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Blood pressure fluctuation			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Deep vein thrombosis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	2	
Flushing			
subjects affected / exposed	5 / 252 (1.98%)	5 / 257 (1.95%)	
occurrences (all)	6	5	
Haematoma			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	

Hot flush			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	9 / 252 (3.57%)	13 / 257 (5.06%)	
occurrences (all)	11	17	
Hypotension			
subjects affected / exposed	20 / 252 (7.94%)	14 / 257 (5.45%)	
occurrences (all)	26	16	
Labile blood pressure			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Orthostatic hypotension			
subjects affected / exposed	3 / 252 (1.19%)	1 / 257 (0.39%)	
occurrences (all)	3	2	
Pallor			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	2	0	
Peripheral coldness			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Periphlebitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Thrombosis			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Varicose vein			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Antibiotic prophylaxis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Bladder neoplasm surgery			

subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Cardiac pacemaker insertion		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Dental implantation		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Hernia repair		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Hip arthroplasty		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Hip surgery		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Hysterectomy		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Interventional procedure		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Knee operation		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Large intestinal polypectomy		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Percutaneous coronary intervention		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Plastic surgery to the face		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Prostatectomy		

subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Skin graft			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Skin neoplasm excision			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	2	
Stent placement			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	2	1	
Suture insertion			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Tooth extraction			
subjects affected / exposed	2 / 252 (0.79%)	3 / 257 (1.17%)	
occurrences (all)	2	3	
Transurethral bladder resection			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Transurethral prostatectomy			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Urethral stent removal			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Varicose vein operation			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 252 (2.38%)	7 / 257 (2.72%)	
occurrences (all)	7	9	
Chest discomfort			

subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Chest pain		
subjects affected / exposed	1 / 252 (0.40%)	4 / 257 (1.56%)
occurrences (all)	1	4
Chills		
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)
occurrences (all)	3	2
Condition aggravated		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Cyst		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Facial pain		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Fatigue		
subjects affected / exposed	10 / 252 (3.97%)	11 / 257 (4.28%)
occurrences (all)	12	13
Feeling cold		
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)
occurrences (all)	0	2
Gait disturbance		
subjects affected / exposed	5 / 252 (1.98%)	2 / 257 (0.78%)
occurrences (all)	6	2
Hernia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Influenza like illness		
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)
occurrences (all)	1	2
Malaise		
subjects affected / exposed	6 / 252 (2.38%)	7 / 257 (2.72%)
occurrences (all)	7	8
Oedema		

subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 2	1 / 257 (0.39%) 1	
Oedema peripheral subjects affected / exposed occurrences (all)	14 / 252 (5.56%) 15	3 / 257 (1.17%) 3	
Pain subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 2	0 / 257 (0.00%) 0	
Peripheral swelling subjects affected / exposed occurrences (all)	6 / 252 (2.38%) 6	1 / 257 (0.39%) 1	
Pyrexia subjects affected / exposed occurrences (all)	5 / 252 (1.98%) 6	2 / 257 (0.78%) 2	
Sensation of foreign body subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 2	0 / 257 (0.00%) 0	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 2	0 / 257 (0.00%) 0	
Seasonal allergy subjects affected / exposed occurrences (all)	3 / 252 (1.19%) 3	1 / 257 (0.39%) 1	
Social circumstances Bereavement subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Decrease of autonomy subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 2	2 / 257 (0.78%) 2	
Pruritus genital			

subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Testicular cyst			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Vaginal haemorrhage			
subjects affected / exposed	3 / 252 (1.19%)	0 / 257 (0.00%)	
occurrences (all)	3	0	
Vulvovaginal burning sensation			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal pain			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Choking			
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)	
occurrences (all)	0	2	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences (all)	3	0	
Cough			
subjects affected / exposed	24 / 252 (9.52%)	13 / 257 (5.06%)	
occurrences (all)	29	17	
Dysphonia			
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)	
occurrences (all)	1	2	
Dyspnoea			
subjects affected / exposed	3 / 252 (1.19%)	1 / 257 (0.39%)	
occurrences (all)	3	1	
Epistaxis			

subjects affected / exposed	3 / 252 (1.19%)	2 / 257 (0.78%)
occurrences (all)	4	3
Increased upper airway secretion		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Lower respiratory tract congestion		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Nasal congestion		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Nasal polyps		
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)
occurrences (all)	2	0
Oropharyngeal pain		
subjects affected / exposed	3 / 252 (1.19%)	4 / 257 (1.56%)
occurrences (all)	3	4
Productive cough		
subjects affected / exposed	6 / 252 (2.38%)	4 / 257 (1.56%)
occurrences (all)	6	5
Pulmonary embolism		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Rales		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Respiratory disorder		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Respiratory tract congestion		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Rhinorrhoea		
subjects affected / exposed	0 / 252 (0.00%)	3 / 257 (1.17%)
occurrences (all)	0	3
Wheezing		

subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	2 / 257 (0.78%) 2	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	5 / 252 (1.98%)	4 / 257 (1.56%)	
occurrences (all)	5	5	
Abnormal dreams			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Affective disorder			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Aggression			
subjects affected / exposed	5 / 252 (1.98%)	9 / 257 (3.50%)	
occurrences (all)	7	11	
Agitation			
subjects affected / exposed	15 / 252 (5.95%)	21 / 257 (8.17%)	
occurrences (all)	21	23	
Alexithymia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Anger			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	2	
Anxiety			
subjects affected / exposed	9 / 252 (3.57%)	10 / 257 (3.89%)	
occurrences (all)	9	10	
Borderline personality disorder			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	13 / 252 (5.16%)	11 / 257 (4.28%)	
occurrences (all)	14	13	
Delirium			
subjects affected / exposed	3 / 252 (1.19%)	1 / 257 (0.39%)	
occurrences (all)	3	1	

Delusion		
subjects affected / exposed	1 / 252 (0.40%)	3 / 257 (1.17%)
occurrences (all)	1	3
Depressed mood		
subjects affected / exposed	5 / 252 (1.98%)	11 / 257 (4.28%)
occurrences (all)	5	12
Depression		
subjects affected / exposed	7 / 252 (2.78%)	2 / 257 (0.78%)
occurrences (all)	7	2
Dermatillomania		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Disorientation		
subjects affected / exposed	6 / 252 (2.38%)	2 / 257 (0.78%)
occurrences (all)	7	2
Dissociative amnesia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Emotional disorder		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	2	0
Emotional distress		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Fear		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Frustration tolerance decreased		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Hallucination		
subjects affected / exposed	3 / 252 (1.19%)	1 / 257 (0.39%)
occurrences (all)	3	1
Hallucination, auditory		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1

Hallucination, visual		
subjects affected / exposed	1 / 252 (0.40%)	3 / 257 (1.17%)
occurrences (all)	1	3
Insomnia		
subjects affected / exposed	11 / 252 (4.37%)	3 / 257 (1.17%)
occurrences (all)	13	3
Logorrhoea		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Mood swings		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Neuropsychiatric symptoms		
subjects affected / exposed	8 / 252 (3.17%)	7 / 257 (2.72%)
occurrences (all)	11	8
Obsessive-compulsive disorder		
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)
occurrences (all)	2	0
Panic attack		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Paranoia		
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)
occurrences (all)	1	2
Psychotic disorder		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Restlessness		
subjects affected / exposed	5 / 252 (1.98%)	8 / 257 (3.11%)
occurrences (all)	10	9
Sleep disorder		
subjects affected / exposed	4 / 252 (1.59%)	1 / 257 (0.39%)
occurrences (all)	6	1
Suicidal ideation		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1

Tearfulness subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 2	1 / 257 (0.39%) 1	
Product issues Device breakage subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Hepatobiliary disorders Hepatic cyst subjects affected / exposed occurrences (all) Hepatorenal syndrome subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1 1 / 252 (0.40%) 1	0 / 257 (0.00%) 0 0 / 257 (0.00%) 0	
Investigations Amylase subjects affected / exposed occurrences (all) Bence Jones protein urine present subjects affected / exposed occurrences (all) Biopsy subjects affected / exposed occurrences (all) Biopsy colon subjects affected / exposed occurrences (all) Blood cholesterol abnormal subjects affected / exposed occurrences (all) Blood folate decreased subjects affected / exposed occurrences (all) Blood iron decreased subjects affected / exposed occurrences (all) Blood magnesium abnormal	1 / 252 (0.40%) 1 0 / 252 (0.00%) 0 1 / 252 (0.40%) 1 1 / 252 (0.40%) 1 1 / 252 (0.40%) 1 0 / 252 (0.00%) 0 0 / 252 (0.00%) 0 0 / 252 (0.00%) 0 0 / 252 (0.00%) 0	0 / 257 (0.00%) 0 1 / 257 (0.39%) 1 0 / 257 (0.00%) 0 0 / 257 (0.00%) 0 0 / 257 (0.00%) 0 2 / 257 (0.78%) 2 1 / 257 (0.39%) 1	

subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Blood potassium abnormal		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Blood potassium decreased		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Blood pressure abnormal		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Blood pressure measurement		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	3
Blood sodium decreased		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	2	1
Blood thyroid stimulating hormone increased		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Blood triglycerides abnormal		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Body temperature increased		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Cardiac murmur		
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)
occurrences (all)	2	1
Colonoscopy		
subjects affected / exposed	3 / 252 (1.19%)	1 / 257 (0.39%)
occurrences (all)	3	1
Electrocardiogram ambulatory		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1

Full blood count abnormal			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Gastrointestinal examination			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Haemoglobin decreased			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	3	0	
Heart rate decreased			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Heart rate increased			
subjects affected / exposed	3 / 252 (1.19%)	3 / 257 (1.17%)	
occurrences (all)	3	3	
Heart rate irregular			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Heart sounds abnormal			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Prostatic specific antigen increased			
subjects affected / exposed	2 / 252 (0.79%)	2 / 257 (0.78%)	
occurrences (all)	2	2	
Red blood cell sedimentation rate abnormal			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Spinal X-ray			

subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Thyroid function test abnormal subjects affected / exposed occurrences (all)	3 / 252 (1.19%) 3	0 / 257 (0.00%) 0	
Vitamin B12 abnormal subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	5 / 252 (1.98%) 8	8 / 257 (3.11%) 10	
Weight increased subjects affected / exposed occurrences (all)	4 / 252 (1.59%) 4	3 / 257 (1.17%) 3	
X-ray of pelvis and hip subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Injury, poisoning and procedural complications			
Accidental overdose subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 2	0 / 257 (0.00%) 0	
Alcohol poisoning subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	1 / 257 (0.39%) 1	
Ankle fracture subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Arthropod bite subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Cervical vertebral fracture subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Contusion			

subjects affected / exposed	5 / 252 (1.98%)	3 / 257 (1.17%)
occurrences (all)	5	4
Facial bones fracture		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Fall		
subjects affected / exposed	40 / 252 (15.87%)	38 / 257 (14.79%)
occurrences (all)	50	66
Femur fracture		
subjects affected / exposed	3 / 252 (1.19%)	0 / 257 (0.00%)
occurrences (all)	3	0
Head injury		
subjects affected / exposed	2 / 252 (0.79%)	3 / 257 (1.17%)
occurrences (all)	2	3
Hip fracture		
subjects affected / exposed	2 / 252 (0.79%)	3 / 257 (1.17%)
occurrences (all)	2	3
Humerus fracture		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Injury		
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)
occurrences (all)	0	2
Joint dislocation		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Joint injury		
subjects affected / exposed	2 / 252 (0.79%)	3 / 257 (1.17%)
occurrences (all)	2	3
Laceration		
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)
occurrences (all)	2	1
Ligament sprain		
subjects affected / exposed	2 / 252 (0.79%)	3 / 257 (1.17%)
occurrences (all)	2	3
Limb injury		

subjects affected / exposed	3 / 252 (1.19%)	2 / 257 (0.78%)
occurrences (all)	4	2
Muscle strain		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Overdose		
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)
occurrences (all)	0	5
Poisoning		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Post lumbar puncture syndrome		
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)
occurrences (all)	1	2
Procedural pain		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Radius fracture		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Rib fracture		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Skeletal injury		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Skin abrasion		
subjects affected / exposed	0 / 252 (0.00%)	3 / 257 (1.17%)
occurrences (all)	0	3
Skin wound		
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)
occurrences (all)	1	2
Spinal fracture		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Thermal burn		

subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Toxicity to various agents subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Upper limb fracture subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 2	2 / 257 (0.78%) 2	
Wound subjects affected / exposed occurrences (all)	4 / 252 (1.59%) 4	3 / 257 (1.17%) 3	
Wrist fracture subjects affected / exposed occurrences (all)	3 / 252 (1.19%) 3	2 / 257 (0.78%) 3	
Congenital, familial and genetic disorders Type V hyperlipidaemia subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Cardiac disorders Acute coronary syndrome subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Angina pectoris subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Atrial Fibrillation subjects affected / exposed occurrences (all)	3 / 252 (1.19%) 3	3 / 257 (1.17%) 3	
Atrioventricular block complete subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Atrioventricular block first degree subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 2	1 / 257 (0.39%) 1	
Bradycardia			

subjects affected / exposed	4 / 252 (1.59%)	1 / 257 (0.39%)	
occurrences (all)	4	1	
Cardiac arrest			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Cardiac disorder			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Cardiac failure			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Cardiac fibrillation			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Coronary artery disease			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Mitral valve incompetence			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Myocardial infarction			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Palpitations			
subjects affected / exposed	1 / 252 (0.40%)	3 / 257 (1.17%)	
occurrences (all)	3	3	
Sinus bradycardia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	2 / 252 (0.79%)	4 / 257 (1.56%)	
occurrences (all)	2	6	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 252 (0.00%)	3 / 257 (1.17%)	
occurrences (all)	0	3	

Aphasia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	2
Aphonia		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Apraxia		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Ataxia		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Balance disorder		
subjects affected / exposed	4 / 252 (1.59%)	2 / 257 (0.78%)
occurrences (all)	4	2
Burning sensation		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Clonus		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Cognitive disorder		
subjects affected / exposed	10 / 252 (3.97%)	13 / 257 (5.06%)
occurrences (all)	12	13
Dementia Alzheimer's type		
subjects affected / exposed	5 / 252 (1.98%)	6 / 257 (2.33%)
occurrences (all)	6	9
Depressed level of consciousness		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Disturbance in attention		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Dizziness		
subjects affected / exposed	30 / 252 (11.90%)	29 / 257 (11.28%)
occurrences (all)	39	40

Drooling		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Dysarthria		
subjects affected / exposed	2 / 252 (0.79%)	2 / 257 (0.78%)
occurrences (all)	2	2
Dyspraxia		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Epilepsy		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Facial paralysis		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Headache		
subjects affected / exposed	20 / 252 (7.94%)	19 / 257 (7.39%)
occurrences (all)	27	22
Hypersomnia		
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)
occurrences (all)	2	1
Hypoaesthesia		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Hyporeflexia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Hypotonia		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Lethargy		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Loss of consciousness		
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)
occurrences (all)	0	3

Memory impairment		
subjects affected / exposed	1 / 252 (0.40%)	3 / 257 (1.17%)
occurrences (all)	1	3
Migraine		
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)
occurrences (all)	2	2
Myoclonus		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Neuralgia		
subjects affected / exposed	3 / 252 (1.19%)	0 / 257 (0.00%)
occurrences (all)	3	0
Paraesthesia		
subjects affected / exposed	3 / 252 (1.19%)	3 / 257 (1.17%)
occurrences (all)	3	3
Poor quality sleep		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Presyncope		
subjects affected / exposed	2 / 252 (0.79%)	2 / 257 (0.78%)
occurrences (all)	3	2
Reduced facial expression		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Resting tremor		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Restless legs syndrome		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Sciatica		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Seizure		
subjects affected / exposed	3 / 252 (1.19%)	0 / 257 (0.00%)
occurrences (all)	7	0

Sleep phase rhythm disturbance subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Somnolence subjects affected / exposed occurrences (all)	3 / 252 (1.19%) 3	4 / 257 (1.56%) 4	
Speech disorder subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	1 / 257 (0.39%) 1	
Syncope subjects affected / exposed occurrences (all)	12 / 252 (4.76%) 18	9 / 257 (3.50%) 13	
Tension headache subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 2	1 / 257 (0.39%) 1	
Transient ischaemic attack subjects affected / exposed occurrences (all)	3 / 252 (1.19%) 3	1 / 257 (0.39%) 1	
Tremor subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	3 / 257 (1.17%) 3	
Visual field defect subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Vlth nerve paralysis subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	4 / 257 (1.56%) 5	
Anaemia macrocytic subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	1 / 257 (0.39%) 1	
Iron deficiency anaemia			

subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Lymphadenitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Lymphadenopathy			
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)	
occurrences (all)	1	2	
Pernicious anaemia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Ear pain			
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)	
occurrences (all)	2	1	
Excessive cerumen production			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Hypoacusis			
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)	
occurrences (all)	0	2	
Sudden hearing loss			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	1 / 252 (0.40%)	4 / 257 (1.56%)	
occurrences (all)	1	4	
Vertigo			
subjects affected / exposed	5 / 252 (1.98%)	2 / 257 (0.78%)	
occurrences (all)	7	2	

Eye disorders			
Amblyopia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Cataract			
subjects affected / exposed	5 / 252 (1.98%)	2 / 257 (0.78%)	
occurrences (all)	6	2	
Conjunctival haemorrhage			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Eye allergy			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Eye haemorrhage			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	2	0	
Eye irritation			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Eye movement disorder			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Eye pain			
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)	
occurrences (all)	2	1	
Glaucoma			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Myopia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Ocular hyperaemia			

subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences (all)	2	0	
Presbyopia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Visual acuity reduced			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 252 (0.79%)	5 / 257 (1.95%)	
occurrences (all)	3	8	
Abdominal distension			
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	7 / 252 (2.78%)	6 / 257 (2.33%)	
occurrences (all)	8	6	
Abdominal pain lower			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	3 / 252 (1.19%)	1 / 257 (0.39%)	
occurrences (all)	4	1	
Abdominal tenderness			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Anal incontinence			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Coeliac disease			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	

Colitis		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Constipation		
subjects affected / exposed	5 / 252 (1.98%)	4 / 257 (1.56%)
occurrences (all)	5	5
Diarrhoea		
subjects affected / exposed	19 / 252 (7.54%)	16 / 257 (6.23%)
occurrences (all)	20	19
Dry mouth		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Duodenogastric reflux		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Dyspepsia		
subjects affected / exposed	3 / 252 (1.19%)	3 / 257 (1.17%)
occurrences (all)	3	3
Dysphagia		
subjects affected / exposed	4 / 252 (1.59%)	3 / 257 (1.17%)
occurrences (all)	4	3
Eructation		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Flatulence		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Gastritis		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Gastrointestinal sounds abnormal		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Gastrooesophageal reflux disease		
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)
occurrences (all)	2	0

Gingival bleeding		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Haemorrhoids		
subjects affected / exposed	4 / 252 (1.59%)	1 / 257 (0.39%)
occurrences (all)	4	1
Hiatus hernia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Inguinal hernia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Intestinal metaplasia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Nausea		
subjects affected / exposed	15 / 252 (5.95%)	12 / 257 (4.67%)
occurrences (all)	16	15
Occult blood		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Pharyngo-oesophageal diverticulum		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	2
Proctalgia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Rectal haemorrhage		
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)
occurrences (all)	2	0
Salivary hypersecretion		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	2
Stomatitis		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0

Vomiting			
subjects affected / exposed	19 / 252 (7.54%)	15 / 257 (5.84%)	
occurrences (all)	19	23	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Dry skin			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Eczema			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	2 / 252 (0.79%)	2 / 257 (0.78%)	
occurrences (all)	2	2	
Hyperhidrosis			
subjects affected / exposed	0 / 252 (0.00%)	3 / 257 (1.17%)	
occurrences (all)	0	3	
Ingrowing nail			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Pemphigoid			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	2 / 252 (0.79%)	2 / 257 (0.78%)	
occurrences (all)	3	2	
Psoriasis			
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)	
occurrences (all)	1	2	
Rash			

subjects affected / exposed	5 / 252 (1.98%)	9 / 257 (3.50%)
occurrences (all)	5	10
Rash macular		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Seborrhoeic dermatitis		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Seborrhoeic keratosis		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Skin discolouration		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Skin disorder		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Skin fissures		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Skin irritation		
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)
occurrences (all)	2	2
Skin lesion		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Skin ulcer		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Skin warm		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Stasis dermatitis		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Urticaria		

subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Xeroderma			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Bladder prolapse			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Dysuria			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Globus urinary bladder			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Incontinence			
subjects affected / exposed	3 / 252 (1.19%)	4 / 257 (1.56%)	
occurrences (all)	3	4	
Lower urinary tract symptoms			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Micturition urgency			
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences (all)	2	0	
Pollakiuria			
subjects affected / exposed	3 / 252 (1.19%)	6 / 257 (2.33%)	
occurrences (all)	3	6	
Renal cyst			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	

Renal failure subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	1 / 257 (0.39%) 1	
Renal impairment subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Renal pain subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Ureterolithiasis subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Urinary incontinence subjects affected / exposed occurrences (all)	5 / 252 (1.98%) 5	5 / 257 (1.95%) 5	
Urinary tract disorder subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Endocrine disorders Goitre subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Hypothyroidism subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	1 / 257 (0.39%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	14 / 252 (5.56%) 17	16 / 257 (6.23%) 20	
Arthritis subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	2 / 257 (0.78%) 2	
Back pain subjects affected / exposed occurrences (all)	8 / 252 (3.17%) 9	10 / 257 (3.89%) 13	
Bursitis			

subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Coccydynia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Fistula		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Flank pain		
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)
occurrences (all)	1	2
Fracture		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Groin pain		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Intervertebral disc protrusion		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Joint effusion		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Joint stiffness		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Joint swelling		
subjects affected / exposed	7 / 252 (2.78%)	1 / 257 (0.39%)
occurrences (all)	7	1
Low back pain		
subjects affected / exposed	0 / 252 (0.00%)	3 / 257 (1.17%)
occurrences (all)	0	3
Muscle haemorrhage		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Muscle spasms		

subjects affected / exposed	3 / 252 (1.19%)	3 / 257 (1.17%)
occurrences (all)	3	4
Muscular weakness		
subjects affected / exposed	3 / 252 (1.19%)	2 / 257 (0.78%)
occurrences (all)	3	2
Musculoskeletal chest pain		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Musculoskeletal discomfort		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Musculoskeletal pain		
subjects affected / exposed	3 / 252 (1.19%)	5 / 257 (1.95%)
occurrences (all)	3	5
Musculoskeletal stiffness		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Myalgia		
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)
occurrences (all)	1	2
Neck pain		
subjects affected / exposed	3 / 252 (1.19%)	0 / 257 (0.00%)
occurrences (all)	3	0
Osteoarthritis		
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)
occurrences (all)	2	1
Osteoporosis		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Pain in extremity		
subjects affected / exposed	8 / 252 (3.17%)	7 / 257 (2.72%)
occurrences (all)	9	7
Pain in jaw		
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)
occurrences (all)	0	2
Posture abnormal		

subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Rotator cuff syndrome			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Spinal pain			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Tendonitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 252 (2.78%)	9 / 257 (3.50%)	
occurrences (all)	9	10	
Cellulitis			
subjects affected / exposed	5 / 252 (1.98%)	0 / 257 (0.00%)	
occurrences (all)	9	0	
Cystitis			
subjects affected / exposed	4 / 252 (1.59%)	3 / 257 (1.17%)	
occurrences (all)	5	4	
Dental abscess			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)	
occurrences (all)	0	2	
Erysipelas			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Eye infection			
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)	
occurrences (all)	2	1	

Eye infection bacterial		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Fungal infection		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Fungal skin infection		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Gastroenteritis		
subjects affected / exposed	4 / 252 (1.59%)	2 / 257 (0.78%)
occurrences (all)	4	5
Gastroenteritis viral		
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)
occurrences (all)	2	0
Gingivitis		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Haematoma infection		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Helicobacter infection		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Herpes zoster		
subjects affected / exposed	2 / 252 (0.79%)	3 / 257 (1.17%)
occurrences (all)	3	3
Hordeolum		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Infection		
subjects affected / exposed	2 / 252 (0.79%)	2 / 257 (0.78%)
occurrences (all)	2	2
Influenza		
subjects affected / exposed	17 / 252 (6.75%)	11 / 257 (4.28%)
occurrences (all)	19	15

Kidney infection		
subjects affected / exposed	7 / 252 (2.78%)	1 / 257 (0.39%)
occurrences (all)	8	1
Labyrinthitis		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Laryngitis		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Localised infection		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Lower respiratory tract infection		
subjects affected / exposed	10 / 252 (3.97%)	7 / 257 (2.72%)
occurrences (all)	14	8
Nail bed infection		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Onychomycosis		
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)
occurrences (all)	1	2
Oral herpes		
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)
occurrences (all)	2	0
Paronychia		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	2 / 252 (0.79%)	2 / 257 (0.78%)
occurrences (all)	3	3
Pneumonia		
subjects affected / exposed	4 / 252 (1.59%)	0 / 257 (0.00%)
occurrences (all)	4	0
Pseudomonas infection		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0

Pyelonephritis		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Respiratory tract infection		
subjects affected / exposed	1 / 252 (0.40%)	2 / 257 (0.78%)
occurrences (all)	1	4
Sepsis		
subjects affected / exposed	3 / 252 (1.19%)	3 / 257 (1.17%)
occurrences (all)	3	3
Sinusitis		
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)
occurrences (all)	2	1
Skin infection		
subjects affected / exposed	0 / 252 (0.00%)	3 / 257 (1.17%)
occurrences (all)	0	3
Tinea versicolour		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Tooth abscess		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Tooth infection		
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)
occurrences (all)	2	0
Tracheitis		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	2	0
Urinary tract infection		
subjects affected / exposed	25 / 252 (9.92%)	24 / 257 (9.34%)
occurrences (all)	41	40
Urosepsis		
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)
occurrences (all)	1	1
Viral upper respiratory tract infection		
subjects affected / exposed	19 / 252 (7.54%)	24 / 257 (9.34%)
occurrences (all)	21	27

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Wound infection subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 2	
Metabolism and nutrition disorders			
Cachexia subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Decreased appetite subjects affected / exposed occurrences (all)	3 / 252 (1.19%) 3	2 / 257 (0.78%) 2	
Dehydration subjects affected / exposed occurrences (all)	2 / 252 (0.79%) 2	1 / 257 (0.39%) 1	
Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 252 (0.00%) 0	1 / 257 (0.39%) 1	
Fluid intake reduced subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Fluid overload subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Folate deficiency subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	1 / 257 (0.39%) 1	
Glucose tolerance impaired subjects affected / exposed occurrences (all)	1 / 252 (0.40%) 1	0 / 257 (0.00%) 0	
Hypercholesterolaemia subjects affected / exposed occurrences (all)	5 / 252 (1.98%) 7	3 / 257 (1.17%) 4	
Hyperglycaemia			

subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Hyperuricaemia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Hypoglycaemia		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Hypokalaemia		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0
Hyponatraemia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Polydipsia		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Type 2 diabetes mellitus		
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)
occurrences (all)	0	1
Vitamin B12 deficiency		
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)
occurrences (all)	2	1
Vitamin D deficiency		
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)
occurrences (all)	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2013	Inclusion of the NILVAD substudy protocols as amendments to the main protocol.
14 March 2013	The timing of when the study medication is to be taken was changed from with lunch to after breakfast. An explanatory note was added to the sample size estimation. The medical food Souvenaid was excluded from the study. The length of time that a CT/MRI report is valid was extended from 2 to 4 years. The unscheduled termination section was updated to state that removal of patients from the study must be discussed with the Principal Investigator and the Project Coordinator rather than the Scientific Project Manager.
20 September 2013	Combine all of the NILVAD protocols into one NILVAD Complete Protocol (including the main and substudy protocols). To increase the time frame between the screening visit and baseline visit from 21 days to 6 weeks. To specify that patients can be re-screened at any point in the recruitment window. To specify that the principal investigator or study clinician can sign off the Eligibility Screening Form.
11 February 2014	Amendment to the exclusion criteria and approval to enroll subjects requiring more than one agent to control blood pressure. This resulted from international consensus guidelines on the management of hypertension which advocated the use of low dose combination antihypertensive (AH) therapy rather than monotherapy to achieve target blood pressure control in hypertensive patients.
17 September 2015	Addition of the event syncope as an expected adverse reaction to the investigator's brochure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27436668>

<http://www.ncbi.nlm.nih.gov/pubmed/25300460>