Clinical trial results:
A European multicenre 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

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

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 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

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 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
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

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 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

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.	
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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Nilvadipine
Reporting group description: -	
Reporting group title	Placebo
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	2 / 252 (0.79%)	1 / 257 (0.39%)	
occurrences (all)	2	1	
Oedema peripheral			
subjects affected / exposed	14 / 252 (5.56%)	3 / 257 (1.17%)	
occurrences (all)	15	3	
Pain			
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences (all)	2	0	
Peripheral swelling			
subjects affected / exposed	6 / 252 (2.38%)	1 / 257 (0.39%)	
occurrences (all)	6	1	
Pyrexia			
subjects affected / exposed	5 / 252 (1.98%)	2 / 257 (0.78%)	
occurrences (all)	6	2	
Sensation of foreign body			
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences (all)	2	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences (all)	2	0	
Seasonal allergy			
subjects affected / exposed	3 / 252 (1.19%)	1 / 257 (0.39%)	
occurrences (all)	3	1	
Social circumstances			
Bereavement			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Decrease of autonomy			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 252 (0.79%)	2 / 257 (0.78%)	
occurrences (all)	2	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	1 / 252 (0.40%)	2 / 257 (0.78%)	
occurrences (all)	1	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	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	2	1	
Product issues			
Device breakage			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatic cyst			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Hepatorenal syndrome			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Investigations			
Amylase			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Bence Jones protein urine present			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Biopsy			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Biopsy colon			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol abnormal			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Blood folate decreased			
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)	
occurrences (all)	0	2	
Blood iron decreased			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Blood magnesium abnormal			

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	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Thyroid function test abnormal			
subjects affected / exposed	3 / 252 (1.19%)	0 / 257 (0.00%)	
occurrences (all)	3	0	
Vitamin B12 abnormal			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	5 / 252 (1.98%)	8 / 257 (3.11%)	
occurrences (all)	8	10	
Weight increased			
subjects affected / exposed	4 / 252 (1.59%)	3 / 257 (1.17%)	
occurrences (all)	4	3	
X-ray of pelvis and hip			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	2 / 252 (0.79%)	0 / 257 (0.00%)	
occurrences (all)	2	0	
Alcohol poisoning			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Ankle fracture			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Arthropod bite			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Cervical vertebral fracture			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	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	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Toxicity to various agents			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Upper limb fracture			
subjects affected / exposed	2 / 252 (0.79%)	2 / 257 (0.78%)	
occurrences (all)	2	2	
Wound			
subjects affected / exposed	4 / 252 (1.59%)	3 / 257 (1.17%)	
occurrences (all)	4	3	
Wrist fracture			
subjects affected / exposed	3 / 252 (1.19%)	2 / 257 (0.78%)	
occurrences (all)	3	3	
Congenital, familial and genetic disorders			
Type V hyperlipidaemia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Angina pectoris			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Atrial Fibrillation			
subjects affected / exposed	3 / 252 (1.19%)	3 / 257 (1.17%)	
occurrences (all)	3	3	
Atrioventricular block complete			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Atrioventricular block first degree			
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)	
occurrences (all)	2	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	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	3 / 252 (1.19%)	4 / 257 (1.56%)	
occurrences (all)	3	4	
Speech disorder			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Syncope			
subjects affected / exposed	12 / 252 (4.76%)	9 / 257 (3.50%)	
occurrences (all)	18	13	
Tension headache			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	2	1	
Transient ischaemic attack			
subjects affected / exposed	3 / 252 (1.19%)	1 / 257 (0.39%)	
occurrences (all)	3	1	
Tremor			
subjects affected / exposed	1 / 252 (0.40%)	3 / 257 (1.17%)	
occurrences (all)	1	3	
Visual field defect			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
VIth nerve paralysis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 252 (0.00%)	4 / 257 (1.56%)	
occurrences (all)	0	5	
Anaemia macrocytic			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	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	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Renal impairment			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Renal pain			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Ureterolithiasis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	5 / 252 (1.98%)	5 / 257 (1.95%)	
occurrences (all)	5	5	
Urinary tract disorder			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 252 (5.56%)	16 / 257 (6.23%)	
occurrences (all)	17	20	
Arthritis			
subjects affected / exposed	0 / 252 (0.00%)	2 / 257 (0.78%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	8 / 252 (3.17%)	10 / 257 (3.89%)	
occurrences (all)	9	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	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Wound infection			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	3 / 252 (1.19%)	2 / 257 (0.78%)	
occurrences (all)	3	2	
Dehydration			
subjects affected / exposed	2 / 252 (0.79%)	1 / 257 (0.39%)	
occurrences (all)	2	1	
Diabetes mellitus			
subjects affected / exposed	0 / 252 (0.00%)	1 / 257 (0.39%)	
occurrences (all)	0	1	
Fluid intake reduced			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Fluid overload			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Folate deficiency			
subjects affected / exposed	1 / 252 (0.40%)	1 / 257 (0.39%)	
occurrences (all)	1	1	
Glucose tolerance impaired			
subjects affected / exposed	1 / 252 (0.40%)	0 / 257 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia			
subjects affected / exposed	5 / 252 (1.98%)	3 / 257 (1.17%)	
occurrences (all)	7	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