Clinical trial results:
Efficacy and safety of 3 doses of S 38093 (2, 5 and 20 mg/day) versus placebo, in co-administration with donepezil (10 mg/day) in patients with moderate Alzheimer's Disease.
A 24-week international, multi-centre, randomised, double-blind, placebo-controlled phase IIb study.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-005862-40
Trial protocol	DE AT FI ES GB SE PT SK IT PL
Global end of trial date	29 January 2015

Results information

Result version number	v1 (current)
This version publication date	04 May 2016
First version publication date	04 May 2016

Trial information

Trial identification

Sponsor protocol code	CL2-38093-012

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, 33 155724366, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, 33 155724366, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2015
Global end of trial reached?	Yes
Global end of trial date	29 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of 3 fixed doses of S 38093 (2, 5 and 20 mg/ day) versus placebo, in co-administration with donepezil 10 mg/day, after 24 weeks of treatment, on cognitive performance measured with the ADAS-Cog 11-items in patients with moderate Alzheimer's Disease

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator:

Placebo

Actual start date of recruitment	04 October 2012
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	Argentina: 44
Country: Number of subjects enrolled	Australia: 52
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Brazil: 41
Country: Number of subjects enrolled	Canada: 35
Country: Number of subjects enrolled	Finland: 15
Country: Number of subjects enrolled	Germany: 63
Country: Number of subjects enrolled	Italy: 76
Country: Number of subjects enrolled	Mexico: 48
Country: Number of subjects enrolled	Poland: 130
Country: Number of subjects enrolled	Portugal: 42
Country: Number of subjects enrolled	Slovakia: 60
Country: Number of subjects enrolled	Spain: 115
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	United Kingdom: 67

Worldwide total number of subjects	806
EEA total number of subjects	586

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)	138
From 65 to 84 years	640
85 years and over	28

Subject disposition

Recruitment

Recruitment details:

Investigators were neuropsychiatrists, neurologists or geriatricians

Pre-assignment

Screening details:

Out-patients aged 55-90 years (Amendment n°6), school education ≥ 4 years, with memory impairment (DSM-IV-TR criteria for dementia of AD type and NINCDS/ADRDA criteria for probable AD), MMSE at selection = 12-20 inclusive, brain MRI at selection, identified informant, and stable donepezil 10 mg/day for at least 3 months before selection.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The study products of identical appareance, S 38093 2 mg, S38093 5 mg, S38093 20 mg or placebo, were assigned by a balanced, non-adaptive randomisation, with stratification by country. Treatment randomisation and allocations centralised (Interactive Response System).

Arms

Are arms mutually exclusive?	Yes
Arm title	S 38093 2 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S 38093 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One oral film-coated tablet of S 38093 2 mg, with a glass of water, once a day, upon waking in the morning. In addition, the patients had to take 1 tablet of donepezil (10mg) orally once daily.

Arm title	S 38093 5 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S 38093 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One oral film-coated tablet of S 38093 5 mg, with a glass of water, once a day, upon waking in the morning. In addition, the patients had to take 1 tablet of donepezil (10mg) orally once daily.

Arm title	S 38093 20 mg

Arm description: -

Arm type	Experimental

Investigational medicinal product name	S 38093 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One oral film-coated tablet of S 38093 20 mg, with a glass of water, once a day, upon waking in the morning. In addition, the patients had to take 1 tablet of donepezil (10mg) orally once daily.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

One oral film-coated tablet of Placebo, with a glass of water, once a day, upon waking in the morning. In addition, the patients had to take 1 tablet of donepezil (10mg) orally once daily.

Number of subjects in period 1	S 38093 2 mg	S 38093 5 mg	S 38093 20 mg
Started	201	202	203
Completed	181	178	173
Not completed	20	24	30
Adverse event, serious fatal	1	1	2
Adverse event, non-fatal	8	12	12
Non-medical reason	6	6	8
Protocol deviation	3	5	7
Lack of efficacy	2	-	1

Number of subjects in period 1	Placebo
Started	200
Completed	181
Not completed	19
Adverse event, serious fatal	2
Adverse event, non-fatal	8
Non-medical reason	3
Protocol deviation	6
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	S 38093 2 mg
Reporting group description: -	
Reporting group title	S 38093 5 mg
Reporting group description: -	
Reporting group title	S 38093 20 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	S 38093 2 mg	S 38093 5 mg	S 38093 20 mg
Number of subjects	201	202	203
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	31	39	29
From 65-84 years	160	159	165
85 years and over	10	4	9
Age continuous Units: years			
arithmetic mean	72.7	72.1	73.3
standard deviation	± 7.6	± 7.6	± 7.4
Gender categorical Units: Subjects			
Female	129	130	131
Male	72	72	72

Reporting group values	Placebo	Total	
Number of subjects	200	806	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	39	138	
From 65-84 years	156	640	

85 years and over	5	28	

Age continuous			
Units: years			
arithmetic mean	72.5		
standard deviation	± 8.3	-	
Gender categorical			
Units: Subjects			
Female	114	504	
Male	86	302	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients of the Randomised Set having taken at least one dose of study drug and having a value at baseline and at least one post-baseline value for the primary criterion.

Reporting group values	Full Analysis Set		
Number of subjects	765		
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)	132		
From 65-84 years	606		
85 years and over	27		
Age continuous			
Units: years			
arithmetic mean	72.6		
standard deviation	± 7.7		
Gender categorical			
Units: Subjects			
Female	481		
Male	284		

End points

End points reporting groups

Reporting group title	S 38093 2 mg
Reporting group description: -	
Reporting group title	S 38093 5 mg
Reporting group description: -	
Reporting group title	S 38093 20 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients of the Randomised Set having taken at least one dose of study drug and having a value at baseline and at least one post-baseline value for the primary criterion.

Primary: 11-item ADAS-Cog total score

End point title	11-item ADAS-Cog total score

End point description:

End point type	Primary

End point timeframe:

Evaluation at inclusion, week 12 and week 24 or in case of premature withdrawal. The main analytical approach was the change from baseline to W24.

End point values	S 38093 2 mg	S 38093 5 mg	S 38093 20 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	191	192	193	189
Units: no unit				
arithmetic mean (standard error)	1.08 (± 5.07)	1.08 (± 5.93)	0.48 (± 6.26)	0.52 (± 6)

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	S 38093 2 mg v Placebo
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	0.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	1.91
Variability estimate	Standard error of the mean
Dispersion value	0.61

Statistical analysis title	Primary analysis
Comparison groups	S 38093 20 mg v Placebo
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	1.16
Variability estimate	Standard error of the mean
Dispersion value	0.61

Statistical analysis title	Primary analysis
Comparison groups	S 38093 5 mg v Placebo
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.69
Variability estimate	Standard error of the mean
Dispersion value	0.61

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred or worsened or became serious according to the investigator, or upgraded by the Sponsor, between the first study drug intake and the last study drug intake date + 10 days (both included).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	S 38093 2 mg
Reporting group description: -	
Reporting group title	S 38093 5 mg
Reporting group description: -	
Reporting group title	S 38093 20 mg
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	S 38093 2 mg	S 38093 5 mg	S 38093 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 199 (6.03%)	15 / 200 (7.50%)	19 / 202 (9.41%)
number of deaths (all causes)	1	2	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diffuse large B-cell lymphoma stage IV			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			

subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 199 (0.50%)	1 / 200 (0.50%)	2 / 202 (0.99%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	1 / 199 (0.50%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	2 / 199 (1.01%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressive symptom			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			

subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucinations, mixed			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	2 / 202 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 199 (1.01%)	3 / 200 (1.50%)	3 / 202 (1.49%)
occurrences causally related to treatment / all	1 / 2	0 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 199 (0.50%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			

subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory fume inhalation disorder			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 199 (0.50%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular procedure complication			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			

subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			

subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	2 / 202 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia Alzheimer's type			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic seizure			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			

subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinsonism			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	5 / 202 (2.48%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 199 (0.00%)	2 / 200 (1.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Panniculitis			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal failure			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Erysipelas			
subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex encephalitis			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	2 / 202 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Post procedural sepsis			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyelonephritis			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			

subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 199 (0.50%)	0 / 200 (0.00%)	2 / 202 (0.99%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 199 (11.56%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diffuse large B-cell lymphoma stage IV			

subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary fibrosis			

subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Agitation			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delusion			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depressive symptom			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hallucination			

subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hallucinations, mixed				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Insomnia				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Major depression				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				

Contusion				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	4 / 199 (2.01%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				

subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory fume inhalation disorder				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic intracranial haemorrhage				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular procedure complication				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				

subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Angina unstable			
subjects affected / exposed	3 / 199 (1.51%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	2 / 199 (1.01%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cognitive disorder			

subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dementia			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dementia Alzheimer's type			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Grand mal convulsion			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemic seizure			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			

subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parkinsonism			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychomotor hyperactivity			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Faecaloma			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large intestine polyp			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Panniculitis			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal failure				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urethral stenosis				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Muscle haemorrhage				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis perforated				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 199 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Erysipelas			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes simplex encephalitis			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonsillar abscess			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural sepsis			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection bacterial			

subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1.5 %

Non-serious adverse events	S 38093 2 mg	S 38093 5 mg	S 38093 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	102 / 199 (51.26%)	106 / 200 (53.00%)	101 / 202 (50.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 199 (2.51%)	1 / 200 (0.50%)	3 / 202 (1.49%)
occurrences (all)	5	1	3
Hypotension			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	2 / 202 (0.99%)
occurrences (all)	0	0	2
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 199 (0.50%)	3 / 200 (1.50%)	0 / 202 (0.00%)
occurrences (all)	1	3	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 199 (0.50%)	5 / 200 (2.50%)	1 / 202 (0.50%)
occurrences (all)	1	5	1
Fatigue			

subjects affected / exposed	2 / 199 (1.01%)	0 / 200 (0.00%)	5 / 202 (2.48%)
occurrences (all)	2	0	6
Gait disturbance			
subjects affected / exposed	2 / 199 (1.01%)	2 / 200 (1.00%)	0 / 202 (0.00%)
occurrences (all)	2	2	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	7 / 199 (3.52%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences (all)	7	0	1
Agitation			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	6 / 202 (2.97%)
occurrences (all)	0	1	6
Anxiety			
subjects affected / exposed	2 / 199 (1.01%)	5 / 200 (2.50%)	3 / 202 (1.49%)
occurrences (all)	2	5	3
Depression			
subjects affected / exposed	4 / 199 (2.01%)	2 / 200 (1.00%)	0 / 202 (0.00%)
occurrences (all)	4	2	0
Insomnia			
subjects affected / exposed	4 / 199 (2.01%)	1 / 200 (0.50%)	2 / 202 (0.99%)
occurrences (all)	4	1	2
Irritability			
subjects affected / exposed	4 / 199 (2.01%)	2 / 200 (1.00%)	3 / 202 (1.49%)
occurrences (all)	4	2	3
Nightmare			
subjects affected / exposed	2 / 199 (1.01%)	1 / 200 (0.50%)	1 / 202 (0.50%)
occurrences (all)	2	1	1
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	1 / 202 (0.50%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	2 / 199 (1.01%)	2 / 200 (1.00%)	5 / 202 (2.48%)
occurrences (all)	2	2	5
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	1 / 199 (0.50%)	1 / 200 (0.50%)	5 / 202 (2.48%)
occurrences (all)	1	1	5
Fall			
subjects affected / exposed	5 / 199 (2.51%)	13 / 200 (6.50%)	11 / 202 (5.45%)
occurrences (all)	8	13	11
Head injury			
subjects affected / exposed	0 / 199 (0.00%)	3 / 200 (1.50%)	0 / 202 (0.00%)
occurrences (all)	0	3	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 199 (2.01%)	4 / 200 (2.00%)	8 / 202 (3.96%)
occurrences (all)	4	7	8
Headache			
subjects affected / exposed	4 / 199 (2.01%)	7 / 200 (3.50%)	7 / 202 (3.47%)
occurrences (all)	4	9	7
Somnolence			
subjects affected / exposed	3 / 199 (1.51%)	0 / 200 (0.00%)	3 / 202 (1.49%)
occurrences (all)	3	0	3
Tension headache			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 199 (1.01%)	0 / 200 (0.00%)	1 / 202 (0.50%)
occurrences (all)	2	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 199 (4.02%)	1 / 200 (0.50%)	4 / 202 (1.98%)
occurrences (all)	9	1	5
Nausea			
subjects affected / exposed	4 / 199 (2.01%)	5 / 200 (2.50%)	8 / 202 (3.96%)
occurrences (all)	4	5	9
Vomiting			
subjects affected / exposed	2 / 199 (1.01%)	5 / 200 (2.50%)	2 / 202 (0.99%)
occurrences (all)	2	5	2
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	4 / 199 (2.01%)	1 / 200 (0.50%)	1 / 202 (0.50%)
occurrences (all)	4	1	1
Leukocyturia			
subjects affected / exposed	4 / 199 (2.01%)	7 / 200 (3.50%)	7 / 202 (3.47%)
occurrences (all)	5	7	7
Urinary incontinence			
subjects affected / exposed	0 / 199 (0.00%)	1 / 200 (0.50%)	5 / 202 (2.48%)
occurrences (all)	0	1	5
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	3 / 199 (1.51%)	1 / 200 (0.50%)	0 / 202 (0.00%)
occurrences (all)	3	1	0
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 199 (0.50%)	4 / 200 (2.00%)	3 / 202 (1.49%)
occurrences (all)	1	4	3
Gastroenteritis			
subjects affected / exposed	4 / 199 (2.01%)	2 / 200 (1.00%)	0 / 202 (0.00%)
occurrences (all)	4	2	0
Nasopharyngitis			
subjects affected / exposed	4 / 199 (2.01%)	7 / 200 (3.50%)	3 / 202 (1.49%)
occurrences (all)	4	9	3
Upper respiratory tract infection			
subjects affected / exposed	2 / 199 (1.01%)	1 / 200 (0.50%)	6 / 202 (2.97%)
occurrences (all)	2	1	6
Urinary tract infection			
subjects affected / exposed	13 / 199 (6.53%)	9 / 200 (4.50%)	7 / 202 (3.47%)
occurrences (all)	15	10	7
Urinary tract infection bacterial			
subjects affected / exposed	5 / 199 (2.51%)	4 / 200 (2.00%)	2 / 202 (0.99%)
occurrences (all)	6	4	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 199 (1.51%)	2 / 200 (1.00%)	2 / 202 (0.99%)
occurrences (all)	3	2	2

Hypercholesterolaemia			
subjects affected / exposed	3 / 199 (1.51%)	4 / 200 (2.00%)	4 / 202 (1.98%)
occurrences (all)	3	4	4
Hypertriglyceridaemia			
subjects affected / exposed	3 / 199 (1.51%)	4 / 200 (2.00%)	1 / 202 (0.50%)
occurrences (all)	3	4	1
Hypokalaemia			
subjects affected / exposed	3 / 199 (1.51%)	0 / 200 (0.00%)	0 / 202 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 199 (56.78%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 199 (2.01%)		
occurrences (all)	5		
Hypotension			
subjects affected / exposed	4 / 199 (2.01%)		
occurrences (all)	4		
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences (all)	0		
Gait disturbance			
subjects affected / exposed	3 / 199 (1.51%)		
occurrences (all)	3		
Psychiatric disorders			
Aggression			

subjects affected / exposed	4 / 199 (2.01%)		
occurrences (all)	4		
Agitation			
subjects affected / exposed	6 / 199 (3.02%)		
occurrences (all)	6		
Anxiety			
subjects affected / exposed	4 / 199 (2.01%)		
occurrences (all)	4		
Depression			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 199 (1.51%)		
occurrences (all)	3		
Irritability			
subjects affected / exposed	2 / 199 (1.01%)		
occurrences (all)	2		
Nightmare			
subjects affected / exposed	4 / 199 (2.01%)		
occurrences (all)	5		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 199 (1.51%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	3 / 199 (1.51%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	5 / 199 (2.51%)		
occurrences (all)	5		
Head injury			

subjects affected / exposed	1 / 199 (0.50%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 199 (3.02%)		
occurrences (all)	7		
Headache			
subjects affected / exposed	7 / 199 (3.52%)		
occurrences (all)	8		
Somnolence			
subjects affected / exposed	2 / 199 (1.01%)		
occurrences (all)	2		
Tension headache			
subjects affected / exposed	3 / 199 (1.51%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 199 (1.51%)		
occurrences (all)	3		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 199 (2.51%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	3 / 199 (1.51%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	2 / 199 (1.01%)		
occurrences (all)	2		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 199 (1.51%)		
occurrences (all)	3		
Leukocyturia			
subjects affected / exposed	4 / 199 (2.01%)		
occurrences (all)	4		
Urinary incontinence			

subjects affected / exposed	1 / 199 (0.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	3 / 199 (1.51%)		
occurrences (all)	3		
Gastroenteritis			
subjects affected / exposed	0 / 199 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	7 / 199 (3.52%)		
occurrences (all)	9		
Upper respiratory tract infection			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	9 / 199 (4.52%)		
occurrences (all)	9		
Urinary tract infection bacterial			
subjects affected / exposed	5 / 199 (2.51%)		
occurrences (all)	9		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 199 (2.51%)		
occurrences (all)	5		
Hypercholesterolaemia			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	3 / 199 (1.51%)		
occurrences (all)	3		
Hypokalaemia			

subjects affected / exposed occurrences (all)	2 / 199 (1.01%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2013	The non-inclusion criteria referring to the ECG findings (PR< 280 ms was replaced by PR > 280 ms) were corrected. New laboratory assessments (LDL and HDL, in order to complete the lipid metabolism analysis already done with the total cholesterol) were introduced. Anticipated benefits/risks and conditions of use of forbidden concomitant treatment were added in he "background" section. Some scale instructions and worksheets to be used in this study were finalized.
03 July 2013	Withdrawal criterion was updated in accordance with the last version of the Summary of Product Characteristics for donepezil.
13 December 2013	The selection criteria referring to age were updated to include very old patients with Alzheimer's disease (the upper limit to participate to the study was changed from 85 to 90 years old. both inclusive). In order to get a more accurate value for the inclusion of patients, 3 ECGs in close succession were to be performed at the selection visit (ASSE) instead of one. The MRI criteria were updated to allow the inclusion of patients with cerebrovascular disease, a common radiological finding, especially in the elderly, as long as the cerebrovascular lesions were unlikely to contribute to the dementia syndrome. Change in authorised concommitant tretament (antipsychotic treatment with typical or atypical neuroleptics was prohibited anymore before and during the study).
15 April 2014	Due to strategic reasons and recruitment difficulties, the number of planned included patient was updated (around 700 instead of 1000).
22 July 2014	New safety data and information regarding the stage of the other studies, in particular the phase IIb monotherapy study which was ended (CL2-38093-011) were added in the "background" section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported