



Clinical trial results:

Efficacy and safety of 3 doses of S 38093 (2, 5 and 20 mg/day) versus placebo in patients with mild to moderate Alzheimer's disease. A 24-week international, multi-centre, randomised, double-blind, placebo-controlled phase IIb study followed by a 24-week extension period.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2010-024626-37
Trial protocol	DE CZ PT HU BG
Global end of trial date	21 March 2014

Results information

Result version number	v2 (current)
This version publication date	22 July 2016
First version publication date	31 July 2015
Version creation reason	• Correction of full data set Data correction due to a system error in EudraCT – Results

Trial information

Trial identification

Sponsor protocol code	CL2-38093-011
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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 (I.R.I.S.)
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.com
Scientific contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, 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	17 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2013
Global end of trial reached?	Yes
Global end of trial date	21 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial was to assess the efficacy and safety of S 38093 versus placebo in patients with mild to moderate Alzheimer's disease (AD).

Protection of trial subjects:

Reasons could lead to premature discontinuation of treatment:

- Adverse event: any medical reason or circumstance justifying the discontinuation of the treatment in the investigator's opinion. The patient was to be withdrawn from the study in case of a repeated demonstration of a QTcF > 500 ms or a delta > 60 ms over baseline (inclusion) value. The following changes in hepatic enzymes should lead to treatment discontinuation of a study participant:

ALAT or ASAT > 8x ULN.

ALAT or ASAT > 5x ULN for more than 2 weeks.

ALAT or ASAT > 3x ULN and total bilirubin > 2x ULN.

ALAT or ASAT > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

- Protocol deviation: in case of a missing informed consent or if there was any deviation that could compromise the patient's safety.

- Lack of efficacy (in the investigator's opinion).

- Non medical reason (e.g. patient's consent withdrawal).

- Lost to follow-up: when the investigator had no news from the patient, s/he had to make every effort to contact him/her, to establish if the study treatment had been discontinued, obtain information on the reason for the treatment discontinuation, and to suggest the patient to come to an end-of-study visit. If all attempts to contact the participant failed, the investigator could then declare the participant "lost to follow-up". The investigator had to document all attempts in the corresponding medical file.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 October 2011
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	Portugal: 5
Country: Number of subjects enrolled	Czech Republic: 57
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	Bulgaria: 70
Country: Number of subjects enrolled	Germany: 75
Country: Number of subjects enrolled	Hungary: 48

Country: Number of subjects enrolled	Australia: 43
Country: Number of subjects enrolled	Brazil: 53
Country: Number of subjects enrolled	Chile: 65
Country: Number of subjects enrolled	Mexico: 51
Country: Number of subjects enrolled	Romania: 36
Country: Number of subjects enrolled	Russian Federation: 115
Country: Number of subjects enrolled	South Africa: 53
Worldwide total number of subjects	711
EEA total number of subjects	331

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)	112
From 65 to 84 years	588
85 years and over	11

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Six hundred (600) out-patients aged 55 to 85 years with mild to moderate Alzheimer's disease were to be included and randomly assigned either S 38093 2 mg/day or S 38093 5 mg/day or S 38093 20 mg/day or placebo.

Period 1

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

Arms

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

Arm description: -

Arm type	Test drug
Investigational medicinal product name	S 38093
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet, orally, with a glass of water, once a day, upon waking in the morning.

Arm title	S 38093 5 mg
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Arm description: -

Arm type	Test drug
Investigational medicinal product name	S 38093
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet, orally, with a glass of water, once a day, upon waking in the morning.

Arm title	S 38093 20 mg
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Arm description: -

Arm type	Test drug
Investigational medicinal product name	S 38093
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet, orally, with a glass of water, once a day, upon waking in the morning.

Arm title	Placebo
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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 tablet, orally, with a glass of water, once a day, upon waking in the morning.

Number of subjects in period 1	S 38093 2 mg	S 38093 5 mg	S 38093 20 mg
Started	176	175	181
Completed	151	158	162
Not completed	25	17	19
Adverse event, non-fatal	6	6	7
Non-medical reason	14	9	8
Protocol deviation	5	-	3
Lack of efficacy	-	2	1

Number of subjects in period 1	Placebo
Started	179
Completed	162
Not completed	17
Adverse event, non-fatal	6
Non-medical reason	7
Protocol deviation	4
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	176	175	181
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)	22	29	27
From 65-84 years	152	142	151
85 years and over	2	4	3
Age continuous Units: years			
arithmetic mean	73	71.9	72.2
standard deviation	± 7	± 7.2	± 7.2
Gender categorical Units: Subjects			
Female	101	105	120
Male	75	70	61

Reporting group values	Placebo	Total	
Number of subjects	179	711	
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)	34	112	
From 65-84 years	143	588	

85 years and over	2	11	
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Age continuous			
Units: years			
arithmetic mean	71.4		
standard deviation	± 7.2	-	
Gender categorical			
Units: Subjects			
Female	116	442	
Male	63	269	

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	Randomised Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All included patients were randomised (711 patients).	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Consisted of 690 patients	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
Consisted of 569 patients	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Consisted of 709 patients.	

Primary: ADAS-Cog total score

End point title	ADAS-Cog total score
End point description:	
To assess the efficacy of 3 fixed doses of S 38093 (2, 5 and 20 mg/ day) versus placebo after 24 weeks of treatment, on cognitive performance measured with the ADAS-Cog 11-item in patients with mild to moderate AD.	
End point type	Primary
End point timeframe:	
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	153 ^[1]	161 ^[2]	166 ^[3]	161 ^[4]
Units: score				
arithmetic mean (standard deviation)	-0.45 (± 5.32)	0.1 (± 5.53)	-0.12 (± 5.22)	0.34 (± 5.55)

Notes:

[1] - FAS having a value of the change from baseline at W24 of the ADAS-Cog total score

[2] - FAS having a value of the change from baseline at W24 of the ADAS-Cog total score

[3] - FAS having a value of the change from baseline at W24 of the ADAS-Cog total score

Statistical analyses

Statistical analysis title	S 38093 2 mg vs Placebo
Comparison groups	Placebo v S 38093 2 mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Mixed-effects Model Repeated Measures
Parameter estimate	Ajusted Mean difference
Point estimate	-0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0.32
Variability estimate	Standard error of the mean
Dispersion value	0.59

Statistical analysis title	S 38093 20 mg vs Placebo
Comparison groups	Placebo v S 38093 20 mg
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.835
Method	Mixed-effects Model Repeated Measures
Parameter estimate	Ajusted Mean difference
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.78
upper limit	0.51
Variability estimate	Standard error of the mean
Dispersion value	0.58

Statistical analysis title	S 38093 5 mg vs Placebo
Comparison groups	S 38093 5 mg v Placebo

Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed-effects Model Repeated Measures
Parameter estimate	Ajusted Mean difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	0.88
Variability estimate	Standard error of the mean
Dispersion value	0.59

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the 48-week treatment period for S 38093 2mg, 5mg and 20 mg

During the 24-week double-blind treatment period for Placebo

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16
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Reporting groups

Reporting group title	S 38093 2 mg
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	S 38093 20 mg
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Reporting group description: -

Reporting group title	S 38093 5 mg
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Reporting group description: -

Serious adverse events	S 38093 2 mg	Placebo	S 38093 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 176 (14.77%)	12 / 178 (6.74%)	34 / 180 (18.89%)
number of deaths (all causes)	5	0	3
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	2 / 176 (1.14%)	0 / 178 (0.00%)	0 / 180 (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
Breast cancer			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Colon cancer metastatic			

subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Prostate cancer			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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
Prostatic adenoma			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Rectal adenoma			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
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			
Deep vein thrombosis			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 176 (0.57%)	1 / 178 (0.56%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Shock			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Surgical and medical procedures			
Inguinal hernia repair			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Asthenia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Chest pain			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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

Multi-organ failure			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Pyrexia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Sudden death			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Abasia			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Choking			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydropneumothorax			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Pleural effusion			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Pulmonary hypertension			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 176 (0.57%)	1 / 178 (0.56%)	7 / 180 (3.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, visual			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Middle insomnia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Aggression			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			

subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Delirium			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Delusion			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Depressed mood			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Major depression			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 176 (1.14%)	0 / 178 (0.00%)	0 / 180 (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
Blood lactate dehydrogenase increased			

subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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 pressure systolic increased			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate decreased			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 176 (2.84%)	3 / 178 (1.69%)	3 / 180 (1.67%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Laceration			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Alcohol poisoning			

subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Ankle fracture			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Confusion postoperative			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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	1 / 176 (0.57%)	1 / 178 (0.56%)	0 / 180 (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
Hand fracture			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Periorbital contusion			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Procedural haemorrhage			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			

subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Road traffic accident			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Tendon rupture			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Wrist fracture			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Cervical vertebral fracture			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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
Forearm fracture			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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
Subdural haematoma			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			

subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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			
Cardiac failure congestive			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Aortic valve stenosis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block first degree			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Sinus arrhythmia			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular extrasystoles			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			

subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Atrial fibrillation			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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
Right ventricular failure			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia Alzheimer's type			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
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 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Balance disorder			

subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Carotid artery occlusion			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular disorder			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
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 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal disorder			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Hemiparesis			

subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Ataxia			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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
Circadian rhythm sleep disorder			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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
Coordination abnormal			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental impairment			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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
Blood and lymphatic system disorders			
Autoimmune thrombocytopenia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Thrombocytopenia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Deafness bilateral			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tinnitus			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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

Dyspepsia			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolic			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia strangulated			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Intestinal perforation			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Melaena			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Pancreatitis acute			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Hepatobiliary disorders			

Cholecystitis chronic			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Skin ulcer			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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			
Renal failure acute			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Urinary incontinence			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Dupuytren's contracture			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Intervertebral disc degeneration			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			

subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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 pain			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Trigger finger			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 176 (1.14%)	0 / 178 (0.00%)	0 / 180 (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
Herpes zoster ophthalmic			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Infected skin ulcer			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Lobar pneumonia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Pelvic abscess			

subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Peritonitis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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 bacterial			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Pyelonephritis			
subjects affected / exposed	1 / 176 (0.57%)	0 / 178 (0.00%)	0 / 180 (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
Viral infection			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Neurosyphilis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophagia			

subjects affected / exposed	0 / 176 (0.00%)	0 / 178 (0.00%)	0 / 180 (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
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 176 (0.00%)	1 / 178 (0.56%)	0 / 180 (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

Serious adverse events	S 38093 5 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 175 (14.86%)		
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 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer metastatic			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Prostate cancer			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostatic adenoma			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal adenocarcinoma			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal adenoma			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shock			

subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Inguinal hernia repair			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperthermia			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multi-organ failure			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Sudden death			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abasia			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Choking			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hydropneumothorax			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			

subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hallucination, visual			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Middle insomnia			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aggression			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delusion			

subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depressed mood			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Disorientation			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood pressure systolic increased			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Heart rate decreased			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 175 (4.00%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	2 / 175 (1.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Alcohol poisoning			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusion postoperative			

subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hand fracture			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periorbital contusion			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural haemorrhage			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			

subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical vertebral fracture			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Forearm fracture			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Angina unstable				
subjects affected / exposed	0 / 175 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic valve stenosis				
subjects affected / exposed	0 / 175 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block first degree				
subjects affected / exposed	0 / 175 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	1 / 175 (0.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus arrhythmia				
subjects affected / exposed	0 / 175 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular extrasystoles				
subjects affected / exposed	0 / 175 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 175 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 175 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				

subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	3 / 175 (1.71%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	2 / 175 (1.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dementia Alzheimer's type			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Balance disorder			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid artery occlusion			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular disorder			

subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cognitive disorder			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Extrapyramidal disorder			
subjects affected / exposed	0 / 175 (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 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic stroke			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hemiparesis			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ataxia			

subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Circadian rhythm sleep disorder			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coordination abnormal			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental impairment			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Autoimmune thrombocytopenia			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tinnitus			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Retinal vein occlusion			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Visual impairment			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspepsia			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enterocoele			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal hypomotility			

subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia strangulated			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin ulcer			

subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary incontinence			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Dupuytren's contracture			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc degeneration			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Trigger finger			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 175 (0.00%) 0 / 0 0 / 0		
Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 175 (0.00%) 0 / 0 0 / 0		
Herpes zoster ophthalmic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 175 (0.00%) 0 / 0 0 / 0		
Infected skin ulcer subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 175 (0.57%) 0 / 1 0 / 0		
Lobar pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 175 (0.00%) 0 / 0 0 / 0		
Pelvic abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 175 (0.00%) 0 / 0 0 / 0		
Peritonitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 175 (0.57%) 0 / 1 0 / 0		
Pneumonia bacterial subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 175 (0.57%) 0 / 1 0 / 0		
Pyelonephritis			

subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurosyphilis			
subjects affected / exposed	0 / 175 (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	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypophagia			
subjects affected / exposed	1 / 175 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 175 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	S 38093 2 mg	Placebo	S 38093 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	102 / 176 (57.95%)	90 / 178 (50.56%)	126 / 180 (70.00%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 176 (3.98%)	3 / 178 (1.69%)	5 / 180 (2.78%)
occurrences (all)	7	3	5
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	13 / 176 (7.39%)	4 / 178 (2.25%)	16 / 180 (8.89%)
occurrences (all)	14	4	23
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 176 (4.55%)	8 / 178 (4.49%)	12 / 180 (6.67%)
occurrences (all)	9	8	13
Orthostatic hypotension			
subjects affected / exposed	6 / 176 (3.41%)	3 / 178 (1.69%)	6 / 180 (3.33%)
occurrences (all)	6	3	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 176 (1.70%)	4 / 178 (2.25%)	7 / 180 (3.89%)
occurrences (all)	3	5	8
Headache			
subjects affected / exposed	6 / 176 (3.41%)	4 / 178 (2.25%)	6 / 180 (3.33%)
occurrences (all)	6	4	8
Somnolence			
subjects affected / exposed	2 / 176 (1.14%)	6 / 178 (3.37%)	5 / 180 (2.78%)
occurrences (all)	2	6	5
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 176 (3.41%)	4 / 178 (2.25%)	12 / 180 (6.67%)
occurrences (all)	7	4	12
Nausea			
subjects affected / exposed	1 / 176 (0.57%)	3 / 178 (1.69%)	7 / 180 (3.89%)
occurrences (all)	1	3	7
Psychiatric disorders			

Depression subjects affected / exposed occurrences (all)	2 / 176 (1.14%) 2	2 / 178 (1.12%) 2	11 / 180 (6.11%) 11
Anxiety subjects affected / exposed occurrences (all)	1 / 176 (0.57%) 1	3 / 178 (1.69%) 4	8 / 180 (4.44%) 9
Insomnia subjects affected / exposed occurrences (all)	0 / 176 (0.00%) 0	1 / 178 (0.56%) 1	5 / 180 (2.78%) 5
Renal and urinary disorders Leukocyturia subjects affected / exposed occurrences (all)	9 / 176 (5.11%) 9	3 / 178 (1.69%) 3	8 / 180 (4.44%) 9
Infections and infestations Bacteriuria subjects affected / exposed occurrences (all)	5 / 176 (2.84%) 5	5 / 178 (2.81%) 5	2 / 180 (1.11%) 2
Urinary tract infection bacterial subjects affected / exposed occurrences (all)	6 / 176 (3.41%) 8	3 / 178 (1.69%) 3	4 / 180 (2.22%) 4
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 176 (1.70%) 3	2 / 178 (1.12%) 2	8 / 180 (4.44%) 8
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 176 (2.27%) 4	0 / 178 (0.00%) 0	8 / 180 (4.44%) 8
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	9 / 176 (5.11%) 9	3 / 178 (1.69%) 4	4 / 180 (2.22%) 5
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	9 / 176 (5.11%) 11	2 / 178 (1.12%) 2	7 / 180 (3.89%) 9

Non-serious adverse events	S 38093 5 mg		
Total subjects affected by non-serious adverse events subjects affected / exposed	115 / 175 (65.71%)		

Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	2 / 175 (1.14%) 2		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	15 / 175 (8.57%) 16		
Vascular disorders Hypertension subjects affected / exposed occurrences (all) Orthostatic hypotension subjects affected / exposed occurrences (all)	8 / 175 (4.57%) 8 3 / 175 (1.71%) 4		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	6 / 175 (3.43%) 7 7 / 175 (4.00%) 7 4 / 175 (2.29%) 4		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	3 / 175 (1.71%) 3 5 / 175 (2.86%) 5		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Anxiety	4 / 175 (2.29%) 4		

subjects affected / exposed occurrences (all)	5 / 175 (2.86%) 5		
Insomnia subjects affected / exposed occurrences (all)	7 / 175 (4.00%) 7		
Renal and urinary disorders Leukocyturia subjects affected / exposed occurrences (all)	14 / 175 (8.00%) 15		
Infections and infestations Bacteriuria subjects affected / exposed occurrences (all)	13 / 175 (7.43%) 13		
Urinary tract infection bacterial subjects affected / exposed occurrences (all)	9 / 175 (5.14%) 11		
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 175 (4.00%) 10		
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 175 (1.71%) 3		
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	9 / 175 (5.14%) 9		
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	3 / 175 (1.71%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2011	Amendment No. 1 was applicable only in Czech Republic. The competent Authorities requested that in addition to be at least in personal contact for 10h per week with the patient and to have known him for at least one year, the informant was also to be either in a common household with the patient or to be in daily contact with him.
07 December 2011	Amendment No. 2 concerned all centres in all countries (international amendment). The main changes were: <ul style="list-style-type: none">- Specification of international units for vitamin B12 cut-off levels (in pmol/L instead of pg/mL) in the biological non-inclusion criteria, without change of the cut-off value.- Addition of an antidepressant, agomelatine, to the list of forbidden treatments.- Further explanations concerning the eligibility of the patient for MMSE were added.- Checklist for brain MRI and corresponding MRI non-inclusion criteria had been updated to be adapted to the 1 Tesla machines that were to be used in the study.- MDRDs formula had been corrected since there was an error in the initial protocol.- Addition of heart rate data collection to the vital signs recorded during the study, using the Automatic Blood Pressure Monitor each time the blood pressure was recorded.- For "Surgery for cataract", event that did not require immediate notification, it was specified that it applied only if surgery for cataract was not associated with any worsening after randomisation.- DMC was given access to the study treatment via IRS, and was allowed to recommend continuation of the study with modification(s) on study design.- Some scale instructions and worksheets were updated to be in line with the versions finally used in the study (the scales concerned were MMSE, ADCS-CGIC, ADAS-Cog, NPI).- Additional information on the management of the therapeutics units and dispensing of study treatment.- Administrative changes, correction of typing errors and update on logistics.
03 January 2012	Amendment No. 3, was applicable only in Portugal. The Ethics Committee of Portugal (CEIC) requested that patients previously treated with AChEI and / or memantine and who were non-responders or did not tolerate the treatment, were eligible for selection into the study.
27 April 2012	Amendment No. 4, concerned all centres in all countries (international amendment). The objective of this amendment was to allow patients suffering from mild to moderate Alzheimer's disease, with a slightly higher load of concomitant vascular lesions, to participate in this study. Consequently, the non-inclusion criteria of the brain MRI were modified to allow patients with white matter lesions grade 1 and grade 2 (classified according to the Fazekas scale), common in patients with Alzheimer's disease, to be included in the study. In addition, ADAS-Cog wordlists for recall and recognition tasks were corrected. Additional updates (on drug concentration measurements, glossary and definitions) and corrections of typing errors noted in the protocol were also implemented.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The section NSAE presented EAEs on treatment and included SEAEs. The causality and seriousness of reported SAE can be ultimately upgraded by the sponsor. The sponsor took these decisions to be compliant with the existing ICH E3 Clinical Study Report.

Notes: