Clinical trial results:
MS-SMART: A Multi-Arm Phase IIb Randomised, Double Blind Placebo-Controlled Clinical Trial Comparing The Efficacy of Three Neuroprotective Drugs in Secondary Progressive Multiple Sclerosis

Summary

EudraCT number	2012-005394-31
Trial protocol	GB
Global end of trial date	04 July 2018

Results information

Result version number	v1 (current)
This version publication date	27 December 2019
First version publication date	27 December 2019

Trial information

Trial identification

Sponsor protocol code	12/0219

Additional study identifiers

ISRCTN number	ISRCTN28440672
ClinicalTrials.gov id (NCT number)	NCT01910259
WHO universal trial number (UTN)	-
Other trial identifiers	CinicalTrials.gov: NCT01910259

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, UCL Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Professor Jeremy Chataway , University College London , +44 203 448 3051, jeremy.chataway@uclh.nhs.uk
Scientific contact	Professor Jeremy Chataway , University College London , +44 203 448 3051, jeremy.chataway@uclh.nhs.uk

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	13 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 July 2018
Global end of trial reached?	Yes
Global end of trial date	04 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective - To establish whether a drug, from a panel of 3 leading candidate neuroprotective drugs, slows the rate of brain volume loss in SPMS over 96 weeks using MRI-derived percentage brain volume change (PBVC).

Secondary Progressive Multiple Sclerosis (SPMS) results from progressive nerve death or neuro-degeneration that causes accumulating and irreversible disability characterised by a range of devastating problems affecting walking, balance, vision, cognition, pain control, bladder and bowel function.

MS-SMART will test 3 leading drugs to determine if any are effective at slowing the rate of brain shrinkage compared to placebo. Brain volume loss will be measured using MRI brain scans, which will also advance our understanding of how the drugs are providing neuroprotection in SPMS patients.

Protection of trial subjects:

All 3 drugs used in the trial are in human use and have a good safety record. The participants were instructed to report any side effects/adverse events so that adequate treatment could be provided. The risks were explained in the Participant Information Leaflets.

Three MRI scans were needed and these can cause some discomfort or claustrophobia. Participants unable to tolerate MRIs were excluded from the study. MRI is unsafe with persons who have permanent metal inplants such as pacemakers or permanent hearing aids and therefore, such patients were also excluded. MRI should not be done on pregnant women, therefore, prior to each MRI, women of child bearing potential had a urine pregnancy test to check that they were not pregnant.

At one site participants were invited to take part in a biomarker substudy which involved an injection into the lower part of their back to remove a small amount of cerebrospinal fluid (CSF) for testing. This procedure has the small risk that a leak of cerebrospinal fluid (CSF) may develop after the procedure. Symptoms of this problem may include a persistent headache that does not go away after 1 to 2 days. A CSF leak can be treated with a blood "patch," in which the person's own blood is injected into the area where the leak is occurring in order for it clot and seal the leak. To minimise this risk atraumatic needles were used. This information was explained in the patient information leaflets.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	18 December 2014
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	United Kingdom: 445
Worldwide total number of subjects	445
EEA total number of subjects	445

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)	435
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

445 patients were randomised between January 2015 and June 2016.

Pre-assignment

Screening details:

Before invitation to clinic for a full screening and consent visit, research staff checked the eligibility criteria that could be easily established, such as age and medications taken. This saved many people the inconvenience of a hospital visit and potential disappointment that they attended a clinic visit only to find out they were not eligible.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo –1 capsule twice per day for 2 years (1 capsule once per day for first 4 weeks).

Identical placebo to match the 3 active drugs was manufactured by the same manufacturer over-encapsulating the IMPs. An equivalent amount of inert excipient was used in place of the active ingredients. The placebo was packaged for the trial by a MIA IMP holder third party manufacturer in UK.

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

Dosage and administration details:

Matched placebo twice per day for 2 years (1 capsule a day for first 4 weeks)

Arm title	Amiloride

Arm description:

Amiloride HCL 5 mg twice per day for 2 years (5 mg once per day for first 4 weeks).

For the purpose of the trial commercial Amiloride was over-encapsulated by a third party manufacturer holding a MIA IMP in conformance with EU cGMP, in order to achieve the blinding.

Arm type	Experimental
Investigational medicinal product name	Amiloride
Investigational medicinal product code	
Other name	Amiloride HCL
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Amiloride HCL 5 mg twice per day for 2 years (5 mg once per day for first 4 weeks).

Arm title	Riluzole

Arm description:

Riluzole 50 mg twice per day for 2 years (50 mg once per day for first 4 weeks).

For the purpose of the trial commercial Rilutek was over-encapsulated by a third party manufacturer holding a MIA IMP in conformance with EU cGMP, in order to achieve the blinding.

Arm type	Experimental
Investigational medicinal product name	Riluzole
Investigational medicinal product code	
Other name	Rilutek
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Riluzole 50 mg twice per day for 2 years (50 mg once per day for first 4 weeks).

Arm title	Fluoxetine

Arm description:

Fluoxetine 20 mg twice per day for 2 years (20 mg once per day for first 4 weeks).

Fluoxetine 20mg capsules was over-encapsulated by a third party manufacturer holding a MIA IMP in conformance with EU cGMP, in order to achieve the blinding.

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

Dosage and administration details:

Fluoxetine 20 mg twice per day for 2 years (20 mg once per day for first 4 weeks).

Number of subjects in period 1	Placebo	Amiloride	Riluzole
Started	112	111	111
Completed	105	105	101
Not completed	7	6	10
Adverse event, serious fatal	-	1	1
Consent withdrawn by subject	3	2	6
Physician decision	-	-	1
Lost to follow-up	4	3	2

Number of subjects in period 1	Fluoxetine
Started	111
Completed	102
Not completed	9
Adverse event, serious fatal	1
Consent withdrawn by subject	4
Physician decision	-
Lost to follow-up	4

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Placebo –1 capsule twice per day for 2 years (1 capsule once per day for first 4 weeks).

Identical placebo to match the 3 active drugs was manufactured by the same manufacturer over-encapsulating the IMPs. An equivalent amount of inert excipient was used in place of the active ingredients. The placebo was packaged for the trial by a MIA IMP holder third party manufacturer in UK.

Reporting group title	Amiloride

Reporting group description:

Amiloride HCL 5 mg twice per day for 2 years (5 mg once per day for first 4 weeks).

For the purpose of the trial commercial Amiloride was over-encapsulated by a third party manufacturer holding a MIA IMP in conformance with EU cGMP, in order to achieve the blinding.

Reporting group title	Riluzole

Reporting group description:

Riluzole 50 mg twice per day for 2 years (50 mg once per day for first 4 weeks).

For the purpose of the trial commercial Rilutek was over-encapsulated by a third party manufacturer holding a MIA IMP in conformance with EU cGMP, in order to achieve the blinding.

Reporting group title	Fluoxetine

Reporting group description:

Fluoxetine 20 mg twice per day for 2 years (20 mg once per day for first 4 weeks).

Fluoxetine 20mg capsules was over-encapsulated by a third party manufacturer holding a MIA IMP in conformance with EU cGMP, in order to achieve the blinding.

Reporting group values	Placebo	Amiloride	Riluzole
Number of subjects	112	111	111
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)	111	110	109
From 65-84 years	1	1	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54.89	54.36	54.10
standard deviation	± 7.16	± 7.18	± 6.75
Gender categorical Units: Subjects			
Female	75	75	74
Male	37	36	37

EDSS score			
EDSS score at randomisation			
Units: EDSS Score			
median	6	6	6
inter-quartile range (Q1-Q3)	5.5 to 6.5	5.5 to 6.5	5.5 to 6.5
Number of years since first symptoms			
The approximate number of years since the patient experienced the first symptoms of the condition.			
Units: Years			
median	19	20	21
inter-quartile range (Q1-Q3)	13 to 29	13 to 30	16 to 26
Number of years since progression			
The approximate number of years since disease progression			
Units: Years			
median	5	6	6
inter-quartile range (Q1-Q3)	3 to 10	4 to 11	4 to 10

Reporting group values	Fluoxetine	Total	
Number of subjects	111	445	
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)	105	435	
From 65-84 years	6	10	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	54.83		
standard deviation	± 7.11	-	
Gender categorical			
Units: Subjects			
Female	74	298	
Male	37	147	
EDSS score			
EDSS score at randomisation			
Units: EDSS Score			
median	6		
inter-quartile range (Q1-Q3)	5.5 to 6.5	-	
Number of years since first symptoms			
The approximate number of years since the patient experienced the first symptoms of the condition.			
Units: Years			
median	21		
inter-quartile range (Q1-Q3)	16 to 29	-	
Number of years since progression			
The approximate number of years since disease progression			
Units: Years			

median	5		
inter-quartile range (Q1-Q3)	3 to 10	-	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo –1 capsule twice per day for 2 years (1 capsule once per day for first 4 weeks).

Identical placebo to match the 3 active drugs was manufactured by the same manufacturer over-encapsulating the IMPs. An equivalent amount of inert excipient was used in place of the active ingredients. The placebo was packaged for the trial by a MIA IMP holder third party manufacturer in UK.

Reporting group title	Amiloride

Reporting group description:

Amiloride HCL 5 mg twice per day for 2 years (5 mg once per day for first 4 weeks).

For the purpose of the trial commercial Amiloride was over-encapsulated by a third party manufacturer holding a MIA IMP in conformance with EU cGMP, in order to achieve the blinding.

Reporting group title	Riluzole

Reporting group description:

Riluzole 50 mg twice per day for 2 years (50 mg once per day for first 4 weeks).

For the purpose of the trial commercial Rilutek was over-encapsulated by a third party manufacturer holding a MIA IMP in conformance with EU cGMP, in order to achieve the blinding.

Reporting group title	Fluoxetine

Reporting group description:

Fluoxetine 20 mg twice per day for 2 years (20 mg once per day for first 4 weeks).

Fluoxetine 20mg capsules was over-encapsulated by a third party manufacturer holding a MIA IMP in conformance with EU cGMP, in order to achieve the blinding.

Primary: Percentage Brain Volume Change

End point title	Percentage Brain Volume Change

End point description:

The primary endpoint was the percentage brain volume change (PBVC) between baseline and 96 weeks, as measured by the Structural Image Evaluation using Normalization of Atrophy (SIENA) method.

End point type	Primary

End point timeframe:

From baseline to 96 weeks

End point values	Placebo	Amiloride	Riluzole	Fluoxetine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	99	99	96
Units: Percentage				
arithmetic mean (standard deviation)	-1.3 (± 1.1)	-1.3 (± 1.0)	-1.4 (± 1.5)	-1.4 (± 1.5)

Statistical analyses

Statistical analysis title	Comparison of Fluoxetine versus Placebo

Statistical analysis description:

A multiple linear regression model was fitted to the PBVC outcome, including trial arm as an explanatory factor variable (with placebo as the reference category), baseline normalised brain volume, and the minimisation variables: age, gender, treatment centre and EDSS at randomisation. Dunnett-adjusted p-values and simultaneous 95% confidence intervals were computed.

Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.863 [2]
Method	Regression, Linear
Parameter estimate	Adjusted mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.3

Notes:

[1] - Note that the results were derived from a single model covering all 393 participants in the analysis set. Therefore the actual number of subjects included in the analysis was 393.
[2] - Dunnett-adjusted p-value to account for multiple testing.

Statistical analysis title	Comparison of Amiloride versus Placebo

Statistical analysis description:

A multiple linear regression model was fitted to the PBVC outcome, including trial arm as an explanatory factor variable (with placebo as the reference category), baseline normalised brain volume, and the minimisation variables: age, gender, treatment centre and EDSS at randomisation. Dunnett-adjusted p-values and simultaneous 95% confidence intervals were computed.

Comparison groups	Placebo v Amiloride
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.995 [4]
Method	Regression, Linear
Parameter estimate	Adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.5

Notes:

[3] - Note that the results were derived from a single model covering all 393 participants in the analysis set. Therefore the actual number of subjects included in the analysis was 393.
[4] - Dunnett-adjusted p-value to account for multiple testing.

Statistical analysis title	Comparison of Riluzole versus Placebo

Statistical analysis description:

A multiple linear regression model was fitted to the PBVC outcome, including trial arm as an explanatory factor variable (with placebo as the reference category), baseline normalised brain volume, and the minimisation variables: age, gender, treatment centre and EDSS at randomisation. Dunnett-adjusted p-values and simultaneous 95% confidence intervals were computed.

Comparison groups	Riluzole v Placebo

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.771 [6]
Method	Regression, Linear
Parameter estimate	Adjusted mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.3

Notes:

[5] - Note that the results were derived from a single model covering all 393 participants in the analysis set. Therefore the actual number of subjects included in the analysis was 393.
[6] - Dunnett-adjusted p-value to account for multiple testing.

Secondary: Number of new or enlarging T2 lesions

End point title	Number of new or enlarging T2 lesions

End point description:

End point type	Secondary

End point timeframe:

From baseline to 96 weeks.

End point values	Placebo	Amiloride	Riluzole	Fluoxetine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	101	100	99
Units: Number per patient				
arithmetic mean (standard deviation)	3.0 (± 6.9)	3.7 (± 8.1)	2.8 (± 5.7)	1.8 (± 5.3)

Statistical analyses

Statistical analysis title	Comparison of Amiloride versus Placebo

Statistical analysis description:

An over-dispersed Poisson regression model was fitted to the number of new or enlarging T2 lesions at 96 weeks; with trial arm, baseline T2 lesion volume, and the minimisation factors (age, gender, treatment centre and EDSS at randomisation) included as explanatory variables.

Comparison groups	Placebo v Amiloride
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.291
Method	Over-dispersed Poisson regression
Parameter estimate	Rate Ratio
Point estimate	1.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.83

Notes:

[7] - Note that the results were derived from a single model covering all 400 participants in the analysis set. Therefore the actual number of subjects included in the analysis was 400.

Statistical analysis title	Comparison of Fluoxetine versus Placebo

Statistical analysis description:

An over-dispersed Poisson regression model was fitted to the number of new or enlarging T2 lesions at 96 weeks; with trial arm, baseline T2 lesion volume, and the minimisation factors (age, gender, treatment centre and EDSS at randomisation) included as explanatory variables.

Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.012
Method	Over-dispersed Poisson regression
Parameter estimate	Rate Ratio
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.87

Notes:

[8] - Note that the results were derived from a single model covering all 400 participants in the analysis set. Therefore the actual number of subjects included in the analysis was 400.

Statistical analysis title	Comparison of Riluzole versus Placebo

Statistical analysis description:

An over-dispersed Poisson regression model was fitted to the number of new or enlarging T2 lesions at 96 weeks; with trial arm, baseline T2 lesion volume, and the minimisation factors (age, gender, treatment centre and EDSS at randomisation) included as explanatory variables.

Comparison groups	Placebo v Riluzole
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.814
Method	Over-dispersed Poisson regression
Parameter estimate	Rate Ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.45

Notes:

[9] - Note that the results were derived from a single model covering all 400 participants in the analysis set. Therefore the actual number of subjects included in the analysis was 400.

Secondary: EDSS score

End point title	EDSS score

End point description:

End point type	Secondary

End point timeframe:

From baseline to 96 weeks

End point values	Placebo	Amiloride	Riluzole	Fluoxetine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	100	92	95
Units: EDSS score				
arithmetic mean (standard deviation)	6.0 (± 1.0)	6.0 (± 1.0)	6.0 (± 1.1)	5.9 (± 1.2)

Statistical analyses

Statistical analysis title	Comparison of Fluoxetine versus Placebo

Statistical analysis description:

A multiple linear regression model was fitted to the EDSS score outcome, including trial arm as an explanatory factor variable (with placebo as the reference category), and the minimisation variables: age, gender, treatment centre and EDSS at randomisation.

Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.535
Method	Regression, Linear
Parameter estimate	Adjusted mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.2

Notes:

[10] - Note that the results were derived from a single model covering all 383 participants in the analysis set. Therefore the actual number of subjects included in the analysis was 383.

Statistical analysis title	Comparison of Riluzole versus Placebo

Statistical analysis description:

A multiple linear regression model was fitted to the EDSS score outcome, including trial arm as an explanatory factor variable (with placebo as the reference category), and the minimisation variables: age, gender, treatment centre and EDSS at randomisation.

Comparison groups	Placebo v Riluzole

Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.628
Method	Regression, Linear
Parameter estimate	Adjusted mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2

Notes:

[11] - Note that the results were derived from a single model covering all 383 participants in the analysis set. Therefore the actual number of subjects included in the analysis was 383.

Statistical analysis title	Comparison of Amiloride versus Placebo

Statistical analysis description:

A multiple linear regression model was fitted to the EDSS score outcome, including trial arm as an explanatory factor variable (with placebo as the reference category), and the minimisation variables: age, gender, treatment centre and EDSS at randomisation.

Comparison groups	Placebo v Amiloride
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.609
Method	Regression, Linear
Parameter estimate	Adjusted mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2

Notes:

[12] - Note that the results were derived from a single model covering all 383 participants in the analysis set. Therefore the actual number of subjects included in the analysis was 383.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

January 2015 to July 2018

Adverse event reporting additional description:

Relapses or expected progressive changes due to SPMS were not reported as AEs. Two of the patients randomised to the riluzole treatment arm were prescribed fluoxetine by their GP during follow-up (these were protocol deviations). These two patients experienced a total of 5 adverse events and no serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Amiloride
Reporting group description: -	
Reporting group title	Fluoxetine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Riluzole
Reporting group description: -	

Serious adverse events	Amiloride	Fluoxetine	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 111 (9.01%)	7 / 111 (6.31%)	13 / 112 (11.61%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastic lung cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Vascular disorders			
Intracranial bleed			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Surgical and medical procedures			
Bladder tumour			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Stent procedure (Chest pain)			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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
Uterine prolapse			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
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			
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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
Death			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hyperthemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 112 (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
Swelling of hand			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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 oedema			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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			
Delirium			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 112 (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
major depressive disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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
panic attack			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
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			
Deranged LFTs			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Broken Right Arm			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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
Cut on scalp due to fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Drug toxicity			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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
Fractured right wist			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Fractured vertebrae			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Head injury with 24 hour amnesia			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Head injury with haematoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Pelvic fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic left intra-capsular fracture of neck of femur			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
soft tissue damage due to fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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			
Coronary artery thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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
Fast Atrial Fibrillation			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 112 (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
Hospitalisation with Bradycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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
Ischaemic heart disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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			
Generalised seizure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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
Vasovagal syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Small bowel obstruction			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Volvulus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gall stones			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Hepatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Skin and subcutaneous tissue disorders			
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Bladder stone			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Nephrotic Syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 112 (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
Musculoskeletal and connective tissue disorders			
Low back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	1 / 111 (0.90%)	0 / 112 (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
Infections and infestations			
Chest infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	1 / 111 (0.90%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
E-Coli Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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
Lower respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 111 (1.80%)	0 / 111 (0.00%)	0 / 112 (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
Respiratory failure due to pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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
Right broken hip			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 111 (0.00%)	0 / 112 (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 gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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
Viral infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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

post-operative wound infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)	0 / 111 (0.00%)	0 / 112 (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	Riluzole		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 111 (10.81%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastic lung cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Intracranial bleed			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Bladder tumour			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stent procedure (Chest pain)			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine prolapse			

alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperthemia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Swelling of hand				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Lower respiratory tract infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
alternative assessment type: Non-				

systematic			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
major depressive disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
panic attack			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Deranged LFTs			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Broken Right Arm			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cut on scalp due to fall			
alternative assessment type: Non-			

systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug toxicity				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fractured right wist				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fractured vertebrae				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Head injury with 24 hour amnesia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Head injury with haematoma				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic left intra-capsular fracture of neck of femur				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
soft tissue damage due to fall				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Coronary artery thrombosis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fast Atrial Fibrillation				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hospitalisation with Bradycardia				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic heart disease				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Generalised seizure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vasovagal syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small bowel obstruction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Volvulus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gall stones				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Bladder stone				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephrotic Syndrome				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 111 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Low back pain				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Chest infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
E-Coli Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure due to pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right broken hip			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 111 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
post-operative wound infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Amiloride	Fluoxetine	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 111 (88.29%)	105 / 111 (94.59%)	100 / 112 (89.29%)
Injury, poisoning and procedural complications			
Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 111 (7.21%)	18 / 111 (16.22%)	7 / 112 (6.25%)
occurrences (all)	14	63	10
Nervous system disorders			
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 111 (9.01%)	9 / 111 (8.11%)	4 / 112 (3.57%)
occurrences (all)	10	9	4
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 111 (19.82%)	22 / 111 (19.82%)	20 / 112 (17.86%)
occurrences (all)	28	32	25
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 111 (9.01%)	9 / 111 (8.11%)	9 / 112 (8.04%)
occurrences (all)	10	11	10
Gastrointestinal disorders			
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 111 (4.50%)	12 / 111 (10.81%)	5 / 112 (4.46%)
occurrences (all)	5	14	5
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 111 (11.71%)	16 / 111 (14.41%)	17 / 112 (15.18%)
occurrences (all)	18	27	21
Dry mouth			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 111 (5.41%)	13 / 111 (11.71%)	0 / 112 (0.00%)
occurrences (all)	8	13	0

Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 111 (9.01%)	20 / 111 (18.02%)	9 / 112 (8.04%)
occurrences (all)	15	21	11
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 111 (4.50%)	12 / 111 (10.81%)	3 / 112 (2.68%)
occurrences (all)	5	16	3
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 111 (6.31%)	11 / 111 (9.91%)	3 / 112 (2.68%)
occurrences (all)	7	12	3
Sore throat			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 111 (3.60%)	6 / 111 (5.41%)	5 / 112 (4.46%)
occurrences (all)	4	10	6
Infections and infestations			
Chest infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 111 (6.31%)	6 / 111 (5.41%)	3 / 112 (2.68%)
occurrences (all)	7	8	3
Common cold			
alternative assessment type: Non-systematic			
subjects affected / exposed	25 / 111 (22.52%)	26 / 111 (23.42%)	29 / 112 (25.89%)
occurrences (all)	32	31	48
UTI			
alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 111 (16.22%)	12 / 111 (10.81%)	14 / 112 (12.50%)
occurrences (all)	44	15	25

Non-serious adverse events	Riluzole		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 111 (90.99%)		
Injury, poisoning and procedural complications			

Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 111 (3.60%)		
occurrences (all)	9		
Nervous system disorders			
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 111 (9.01%)		
occurrences (all)	12		
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 111 (19.82%)		
occurrences (all)	30		
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 111 (9.01%)		
occurrences (all)	11		
Gastrointestinal disorders			
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 111 (6.31%)		
occurrences (all)	8		
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	16 / 111 (14.41%)		
occurrences (all)	18		
Dry mouth			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 111 (4.50%)		
occurrences (all)	6		
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 111 (19.82%)		
occurrences (all)	29		

Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Sore throat			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Infections and infestations			
Chest infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 111 (3.60%)		
occurrences (all)	6		
Common cold			
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 111 (19.82%)		
occurrences (all)	32		
UTI			
alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 111 (16.22%)		
occurrences (all)	37		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2013	Substantial Amendment 1 - Addition of new sites.
08 September 2014	Substantial Amendment 3* *Note there is no Sub Amendment 2. The CTA application was made using version 2 of the protocol. Protocol version 2 was not circulated to sites as it was known that following the CTA application changes would be require to the protocol, i.e. protocol V3.
13 October 2015	Substantial Amendment 4 - Eligibility criteria amended to exclude pts on high dose simvastatin, procedural change to CSF sub study and clarification in main PIL about side effects of fluoxetine.
16 May 2017	Substantial amendment 5 - Protocol updated to reflect changes to fluoxetine Summary of Product Characteristics.
22 February 2018	Substantial amendment 6 - To change site Principal Investigator.

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.

NA

Notes: