



Clinical trial results:

A multicentre randomised trial to establish the effect(s) of routine administration of Fluoxetine for six months in patients with a recent stroke.

Summary

EudraCT number	2011-005616-29
Trial protocol	GB
Global end of trial date	16 May 2018

Results information

Result version number	v1 (current)
This version publication date	02 July 2019
First version publication date	02 July 2019
Summary attachment (see zip file)	FOCUS trial_Lancet publication (FOCUS trial_Lancet publication.pdf)

Trial information

Trial identification

Sponsor protocol code	FOCUS2012
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Additional study identifiers

ISRCTN number	ISRCTN83290762
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CTA Number: 01384/0221/001-0001, NIHR Funding code: 13/04/30, REC Number: 11/SS/0100

Notes:

Sponsors

Sponsor organisation name	Academic and Central Office for Research and Development (ACCORD)
Sponsor organisation address	QMRI, 47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Professor Martin Dennis, University of Edinburgh, 0131 465 9617, martin.dennis@ed.ac.uk
Scientific contact	Professor Martin Dennis, University of Edinburgh, 0131 465 9617, martin.dennis@ed.ac.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	21 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2018
Global end of trial reached?	Yes
Global end of trial date	16 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective: Is there a difference in the functional outcome, measured with the modified Rankin score, at 6 months between those treated with fluoxetine (20mg daily) for 6 months after stroke, and those treated with placebo?

Secondary objectives: To establish whether there a difference in: the long term survival; functional outcome; motor function at 6 and 12 months; communication; cognition; aspects of quality of life (mood, fatigue, participation) at 6 and 12 months; cost of health and social care over 6 and 12 months; risk of serious adverse events at 6 and 12 months and number of new diagnosis of depression between those patients treated with fluoxetine versus placebo?

Protection of trial subjects:

The trial was conducted in accordance with all relevant data protection, ethical and regulatory requirements to ensure the privacy and security of patient information and to ensure the rights, safety and well-being of the patients and the quality of the research data.

We sought FOCUS group and public involvement opinion during the development of the protocol and participant materials and created an easy access patient information sheet and consent form for patients with aphasia. We sought to minimise risk and burden to the patient without compromising the scientific rigour of the trial. The side effects of fluoxetine are well recognised. We sought to minimise risk by excluding patients in whom the risks are likely to be greatest e.g. those with previous seizures. Patient follow-up questionnaires were kept to a minimum so that they would not be too burdensome for patients. Any unexpected deterioration in function between the 6 and 12 month assessments, or indication of depression or another post stroke complication, from the information provided in the questionnaire, was fed back to the GPs. We provided a 24/7 helpline for participants, their families and professionals. Also a 24/7 emergency unblinding service.

Background therapy:

Participants received the background therapy determined by the clinical teams in each of our 103 centres.

Evidence for comparator:

Many clinical and preclinical studies have suggested that fluoxetine might improve outcomes after stroke through a range of mechanisms, which include enhancing neuroplasticity and promoting neurogenesis. The results of the FLAME (FLuoxetine for motor recovery After acute ischaemic stroke) trial indicated that fluoxetine enhanced motor recovery. A subsequent Cochrane systematic review³ of SSRIs for stroke recovery identified 52 randomised controlled trials of SSRIs versus controls (in 4060 patients). This review suggested that SSRIs might reduce post-stroke disability, although this estimate was based on a meta-analysis done across various measures of function and greater effects were seen if studies with increased risk of bias were retained and patients with depression were included. Although promising, data from the FLAME trial and the Cochrane review were not sufficiently compelling to alter stroke treatment guidelines or to alleviate concerns that any possible benefits might be offset by serious adverse reactions.⁴ The primary aim of the Fluoxetine Or Control Under Supervision (FOCUS) trial was to ascertain whether patients with a clinical stroke diagnosis would have improved functional outcomes with a 6-month course of fluoxetine compared with placebo. Important secondary aims were to identify any other benefits or harms and to assess whether any benefits persisted from the end of the treatment period to 12 months after stroke.

Actual start date of recruitment	10 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 3127
Worldwide total number of subjects	3127
EEA total number of subjects	3127

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)	849
From 65 to 84 years	1875
85 years and over	403

Subject disposition

Recruitment

Recruitment details:

Between Sept 10, 2012, and March 31, 2017, 3152 patients were consented in 103 UK hospitals and 3127 were enrolled. 25 patients were not enrolled; 15 were identified as ineligible between obtaining consent and randomisation and in nine cases the patients, carer or family member, or their treating clinician changed their mind about participating.

Pre-assignment

Screening details:

We did not require centres to collect information about patients screened for eligibility

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Fluoxetine
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Oxactin 20mg
Investigational medicinal product code	PL 19611/0017
Other name	Fluoxetine 20mg
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

20mg daily for 6 months. Each capsule contains 22.36 mg fluoxetine hydrochloride equivalent to 20 mg fluoxetine.

Each capsule contains 22.36 mg fluoxetine hydrochloride equivalent to 20 mg fluoxetine.

Excipient with known effect: 58 mg of lactose monohydrate per capsule.

List of excipients:

Lactose monohydrate
Microcrystalline cellulose
Crospovidone
Magnesium stearate

Printing Ink –

Shellac
Black Iron Oxide E172
Propylene Glycol E1520
Ammonium Hydroxide E527

Capsule Shell:

Body:
Indigo carmine E132
Yellow Iron oxide E172
Black Iron oxide E172
Titanium dioxide E171
Gelatin

Arm title	Placebo
Arm description: -	
Arm type	Placebo

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

Dosage and administration details:

1 capsule daily orally for 6 months

Number of subjects in period 1	Fluoxetine	Placebo
Started	1564	1563
6 months	1553	1553
12 months	1539	1544
Completed	1539	1544
Not completed	25	19
Consent withdrawn by subject	20	11
Unable to obtain mRS	5	8

Baseline characteristics

Reporting groups

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

Reporting group values	Fluoxetine	Placebo	Total
Number of subjects	1564	1563	3127
Age categorical			
Units: Subjects			
<=70 years	666	664	1330
>70 years	898	899	1797
Age continuous			
Mean age			
Units: years			
arithmetic mean	71.2	71.5	
standard deviation	± 12.4	± 12.1	-
Gender categorical			
Units: Subjects			
Female	589	616	1205
Male	975	947	1922
Ethnicity			
Units: Subjects			
Asian	30	31	61
Black	35	29	64
chinese	0	1	1
White	1495	1493	2988
Other	4	9	13
Marital Status			
Units: Subjects			
Married	879	846	1725
Partner	93	91	184
Divorced or separated	109	100	209
Widowed	337	354	691
Single	124	150	274
Other	22	22	44
Living arrangement			
Units: Subjects			
Living with someone else	1057	1034	2091
Lives alone	485	516	1001
Living in an institution	10	4	14
Other	12	9	21
Employment Status			
Units: Subjects			
Full-time employment	287	258	545
Part-time employment	76	70	146
Retired	1122	1134	2256

Unemployed or disabled	53	60	113
Other	26	41	67
Independent before stroke			
Units: Subjects			
Independent before stroke	1431	1435	2866
Dependent before stroke	133	128	261
Known coronary heart disease			
Units: Subjects			
Yes	281	300	581
No	1283	1263	2546
Stroke diagnosis			
Units: Subjects			
Non-stroke (final diagnosis)	2	2	4
Ischaemic stroke	1408	1404	2812
Intracerebral haemorrhage	154	157	311
OCSF classification of ischaemic strokes			
Units: Subjects			
Total anterior circulation infarct	318	317	635
Partial anterior circulation infarct	561	553	1114
Lacunar infarct	307	283	590
Posterior circulation infarct	191	230	421
Uncertain	33	23	56
Haemorrhagic so no OCSF	154	157	311
Cause of stroke, modified TOAST classification			
Units: Subjects			
Large artery disease	278	234	512
Small vessel disease	252	218	470
Embolism from heart	377	411	788
Another cause	38	35	73
Unknown or uncertain	465	508	973
Haemorrhagic so no TOAST	154	157	311
Ability to walk at baseline - predictive variable			
Units: Subjects			
Able to walk at time of randomisation	435	412	847
Unable to walk at time of randomisation	1129	1151	2280
Predicted 6m probability of a good outcome (mRS0-2)			
Predicted 6m probability of a good outcome (mRS0-2) using SSV			
Units: Subjects			
0.00 to ≤0.15	592	591	1183
>0.15 to 1.00	972	972	1944
Motor deficit at baseli			
Presence of motor deficit			
Units: Subjects			
Yes	1361	1361	2722
No	203	202	405
Depression at baseline			
Depression at baseline reported by patient or proxy			
Units: Subjects			

Yes	26	18	44
No	1538	1545	3083
Current mood on PHQ2 scale			
Current mood on PHQ2 scale			
Units: Subjects			
2 yes responses	81	60	141
1 yes response	136	130	266
0 yes response	1347	1373	2720
Details of enrolment			
Details of enrolment			
Units: Subjects			
Inpatient	1544	1536	3080
Outpatient	20	27	47
Able to lift both arms at baseline - predictive variable			
Units: Subjects			
Able	924	935	1859
Unable	640	628	1268
Able to talk and not confused at baseline			
Units: Subjects			
Able	1166	1164	2330
Unable	398	399	797
Known Ischaemic stroke or TIA			
Units: Subjects			
Yes	274	294	568
No	1290	1269	2559
Known diabetes mellitus			
Units: Subjects			
Yes	337	303	640
No	1227	1260	2487
Known hyponatraemia			
Units: Subjects			
Yes	19	26	45
No	1545	1537	3082
Previous intracranial bleed			
Units: Subjects			
Yes	27	23	50
No	1537	1540	3077
Previous upper GI bleed			
Units: Subjects			
Yes	25	26	51
No	1539	1537	3076
Previous bone fracture			
Units: Subjects			
Yes	241	256	497
No	1323	1307	2630
Previous depression			
Units: Subjects			
Yes	130	123	253
No	1434	1440	2874
Consent from			

Units: Subjects			
Patient	1136	1118	2254
Proxy	428	445	873
Aphasia at baseline			
Aphasia at baseline on NIHSS			
Units: Subjects			
Yes	457	449	906
No	1107	1114	2221
Taking non SSRI at baseline			
Units: Subjects			
Yes	65	77	142
No	1499	1486	2985
Probability of a good outcome (mRS0-2) on SSV			
Probability of a good outcome (mRS0-2) on SSV			
Units: proportion			
median	0.28	0.26	
inter-quartile range (Q1-Q3)	0.07 to 0.63	0.07 to 0.63	-
NIHSS score at baseline			
Total NIHSS score at baseline			
Units: points			
median	6	6	
inter-quartile range (Q1-Q3)	3 to 11	3 to 11	-
Delay since stroke onset to randomisation			
Delay since stroke onset to randomisation			
Units: Days			
arithmetic mean	6.9	7.0	
standard deviation	± 3.6	± 3.6	-

End points

End points reporting groups

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

Primary: Disability on the modified Rankin Scale (mRS) at 6 months

End point title	Disability on the modified Rankin Scale (mRS) at 6 months
End point description: The primary outcome was functional status, measured with the modified Rankin Scale (mRS) at 6 months after randomisation. We performed an ordinal logistic regression adjusted for baseline variables included in our minimisation algorithm. We also carried out unadjusted analysis but this was a secondary analysis.	
End point type	Primary
End point timeframe: At 6 months after randomisation (although we used data captured from 90 days to 12 months after date of randomisation).	

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1564	1563		
Units: 0 to 6				
mRS = 0	114	124		
mRS = 1	302	309		
mRS = 2	156	155		
mRS = 3	518	510		
mRS = 4	121	122		
mRS = 5	213	203		
mRS = 6	129	130		
Missing	11	10		

Statistical analyses

Statistical analysis title	Ordinal analysis of the mRS adjusted
Statistical analysis description: Ordinal analysis of the modified Rankin Scale (mRS) adjusted with logistic regression for the variables included in our minimisation algorithm. 1553 patients had mRS data available in each group; 11 patients in the fluoxetine group and ten in the placebo group had missing mRS data. Common odds ratio 0.951 (95% CI 0.839–1.079), p=0.439; adjusted for baseline variables	
Comparison groups	Fluoxetine v Placebo

Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.439 ^[1]
Method	Ordinal logistic regression
Parameter estimate	Common odds ratio
Point estimate	0.951
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.839
upper limit	1.079

Notes:

[1] - adjusted for baseline variables

Statistical analysis title	Ordinal analysis of 6m mRS unadjusted
Statistical analysis description:	
Ordinal analysis of 6m mRS unadjusted	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.531 ^[2]
Method	Ordinal logistic regression
Parameter estimate	Common odds ratio
Point estimate	0.961
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.848
upper limit	1.089

Notes:

[2] - unadjusted

Secondary: Adverse outcomes by 6 months

End point title	Adverse outcomes by 6 months
End point description:	
The proportion of patients with each safety outcome by group	
End point type	Secondary
End point timeframe:	
by 6 months	

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1564	1563		
Units: Patients				
Any stroke	56	64		
All thrombotic event	78	92		
Ischaemic Stroke	43	45		
Other thrombotic events	20	27		
Acute coronary events	15	23		
All bleeding events	41	38		
Haemorrhagic stroke	7	9		
Upper gastrointestinal bleed	21	16		
Other major bleeds	13	14		
Epileptic seizures	58	40		
Fall with Injury	120	94		
Fractured bone	45	23		
Hyponatraemia<125mmol/L	22	14		
Hyperglycaemia	23	16		
Symptomatic hypoglycaemia	23	13		
New depression	210	269		
New antidepressant	280	357		
attempted or actual suicide	3	2		

Statistical analyses

Statistical analysis title	Any stroke at 6m
Statistical analysis description:	
Any stroke at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4543
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0.8

Statistical analysis title	All Thrombotic events at 6m
Statistical analysis description:	
All Thrombotic events at 6m	
Comparison groups	Placebo v Fluoxetine

Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2677
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.49
upper limit	0.69

Statistical analysis title	Ischaemic Stroke at 6m
Statistical analysis description: Ischaemic Stroke at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8264
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1

Statistical analysis title	Other thrombotic events at 6m
Statistical analysis description: Other thrombotic events at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3025
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.4

Statistical analysis title	Acute coronary events at 6m
Statistical analysis description: Acute coronary events at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.191
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.28
upper limit	0.26

Statistical analysis title	All bleeding events at 6m
Statistical analysis description: All bleeding events at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7346
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	1.29

Statistical analysis title	Haemorrhagic stroke at 6m
Statistical analysis description: Haemorrhagic stroke at 6m	
Comparison groups	Fluoxetine v Placebo

Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6153
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.37

Statistical analysis title	Upper gastronomical bleed at 6m
Statistical analysis description: Upper gastronomical bleed at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4094
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	1.08

Statistical analysis title	other major bleeds at 6m
Statistical analysis description: other major bleeds at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8454
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	0.58

Statistical analysis title	Epileptic seizures at 6m
Statistical analysis description:	
Epileptic seizures at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0651
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	2.37

Statistical analysis title	Fall with injury at 6m
Statistical analysis description:	
Fall with injury at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0663
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	3.43

Statistical analysis title	Fractured bone at 6m
Statistical analysis description:	
Fractured bone at 6m	
Comparison groups	Fluoxetine v Placebo

Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	2.43

Statistical analysis title	Hyponatraemia<125 mmol/L at 6m
Statistical analysis description: Hyponatraemia<125 mmol/L at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1805
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	1.26

Statistical analysis title	Hyperglycaemia at 6m
Statistical analysis description: Hyperglycaemia at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2602
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	1.22

Statistical analysis title	Symptomatic Hypoglycaemia at 6m
Statistical analysis description: Symptomatic Hypoglycaemia at 6m	
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	1.39

Statistical analysis title	New Depression at 6m
Statistical analysis description: New Depression at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0033
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-3.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	-1.26

Statistical analysis title	New antidepressant at 6m
Statistical analysis description: New antidepressant at 6m	
Comparison groups	Fluoxetine v Placebo

Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-4.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.76
upper limit	-2.12

Statistical analysis title	attempted or actual suicide at 6m
Statistical analysis description: attempted or actual suicide at 6m	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.655
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.34

Secondary: Stroke impact scale at 6m		
End point title		Stroke impact scale at 6m
End point description:		
Stroke impact scale domains:		
each heading adjusted - missing pts:		
	Fluoxetine	Placebo
Strength	1551	1549
Hand ability	1550	1545
mobility	1555	1556
motor	1552	1550
daily activities	1563	1550
physical function	1563	1551
memory	1541	1545
communication	1552	1552
emotion	1522	1534
participation	1552	1548
Recovery (VAS)	1548	1554
End point type		Secondary

End point timeframe:
6 months from randomisation

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1564	1563		
Units: units				
median (inter-quartile range (Q1-Q3))				
Strength	56.25 (31.25 to 81.25)	62.50 (37.50 to 81.25)		
Hand ability	45.00 (0.00 to 90.00)	50.00 (0.00 to 90.00)		
Mobility	63.89 (36.11 to 86.11)	63.89 (33.33 to 88.89)		
Motor	54.86 (27.31 to 83.00)	56.78 (28.75 to 82.64)		
Daily activities	62.50 (37.50 to 90.00)	65.00 (35.00 to 90.00)		
Physical function	56.77 (30.38 to 84.31)	58.82 (30.56 to 84.10)		
Memory	82.14 (57.14 to 96.43)	82.14 (57.14 to 96.43)		
Communication	89.29 (67.86 to 100.00)	92.86 (71.43 to 100.00)		
Emotion	75.00 (58.33 to 88.89)	75.00 (58.33 to 88.89)		
Participation	62.50 (37.50 to 87.50)	65.63 (40.63 to 87.50)		
Recovery (VAS)	60.00 (40.00 to 80.00)	60.00 (40.00 to 80.00)		

Statistical analyses

Statistical analysis title	SIS - Strength 6m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7008
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS - Hand Ability 6m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo

Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4824
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS - Mobility 6m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5486
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS - Motor 6m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5125
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS - Daily Activities 6m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6235
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS - Physical function 6m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo

Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5154
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS - Memory 6m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.307
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS - Communication 6m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1919
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS - Emotion 6m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4687
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS - Participation 6m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo

Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2595
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS - Recover (VAS) 6m
Statistical analysis description: Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.982
Method	Wilcoxon (Mann-Whitney)

Secondary: Vitality - subscale of SF36

End point title	Vitality - subscale of SF36
End point description: Vitality - subscale of SF36	
End point type	Secondary
End point timeframe: by 6 months	

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1545	1542		
Units: units				
median (inter-quartile range (Q1-Q3))				
Vitality	56.25 (37.50 to 75.00)	56.25 (43.75 to 75.00)		

Statistical analyses

Statistical analysis title	Vitality 6m
Statistical analysis description: Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo

Number of subjects included in analysis	3087
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6726
Method	Wilcoxon (Mann-Whitney)

Secondary: Mental Health Inventory - 5 item at 6m

End point title	Mental Health Inventory - 5 item at 6m
End point description:	Mental Health Inventory - 5 item at 6m
End point type	Secondary
End point timeframe:	by 6 months

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1538	1541		
Units: units				
median (inter-quartile range (Q1-Q3))				
MHI-5	76.00 (60.00 to 88.00)	72.00 (56.00 to 88.00)		

Statistical analyses

Statistical analysis title	Mental Health Inventory -5
Statistical analysis description:	Comparison of fluoxetine vs Placebo - Mann Whitney test
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3079
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Wilcoxon (Mann-Whitney)

Secondary: Health related quality of life (EurQol - EQ5D-5L) at 6m

End point title	Health related quality of life (EurQol - EQ5D-5L) at 6m
End point description:	Health related quality of life (EurQol - EQ5D-5L) at 6m
End point type	Secondary
End point timeframe:	by 6 months

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1552	1559		
Units: units				
median (inter-quartile range (Q1-Q3))				
EQ5D-5L	0.56 (0.21 to 0.74)	0.56 (0.19 to 0.75)		

Statistical analyses

Statistical analysis title	EQ5D -5L at 6m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5866
Method	Wilcoxon (Mann-Whitney)

Secondary: Disability on the modified Rankin Scale at 12 months by treatment group

End point title	Disability on the modified Rankin Scale at 12 months by treatment group
End point description:	
The primary outcome was functional status, measured with the modified Rankin Scale (mRS) at 12 months after randomisation.	
End point type	Secondary
End point timeframe:	
by 12m	

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1564	1563		
Units: 0-6				
mRS = 0	133	145		
mRS = 1	251	237		
mRS = 2	178	175		
mRS = 3	494	505		
mRS = 4	90	81		
mRS = 5	211	203		

mRS = 6	182	198		
Missing	25	19		

Statistical analyses

Statistical analysis title	Ordinal analysis of the modified Rankin Scale(mRS)
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82 ^[3]
Method	Ordinal logistic regression
Parameter estimate	common odds ratio
Point estimate	1.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.894
upper limit	1.151

Notes:

[3] - Adjusted for minimisation variables

Statistical analysis title	Ordinal analysis of 12m mRS unadjusted
Statistical analysis description:	
Ordinal analysis of 12m mRS unadjusted	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.158 ^[4]
Method	Ordinal logistic regression
Parameter estimate	Common Odd ratio
Point estimate	1.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.879
upper limit	1.215

Notes:

[4] - Unadjusted

Secondary: Stroke impact Scale at 12m

End point title	Stroke impact Scale at 12m
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End point description:

Stroke impact domains

each heading adjusted - missing pts:

Fluoxetine

Placebo

Strength	1529	1532
Hand ability	1530	1530
mobility	1536	1534
motor	1531	1532
daily activities	1534	1530
physical function	1534	1532
memory	1531	1531
communication	1532	1534
emotion	1518	1519
participation	1532	1530
Recovery (VAS)	1540	1539

End point type	Secondary
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End point timeframe:

by 12 months

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1564	1563		
Units: Units				
median (inter-quartile range (Q1-Q3))				
SIS Strength	56.25 (31.25 to 75.00)	56.25 (37.50 to 75.00)		
SIS Hand ability	50.00 (0.00 to 90.00)	50.00 (5.00 to 90.00)		
SIS mobility	66.67 (36.11 to 88.89)	66.67 (38.89 to 88.89)		
SIS motor	55.56 (28.80 to 83.33)	58.61 (31.20 to 83.70)		
SIS Daily activities	67.50 (40.00 to 90.00)	67.50 (40.00 to 90.00)		
SIS Physical function	57.81 (32.81 to 84.24)	60.10 (33.54 to 85.28)		
SIS Memory	78.57 (60.71 to 96.43)	82.14 (57.14 to 96.43)		
SIS Communication	89.29 (67.86 to 100.00)	89.29 (71.43 to 100.00)		
SIS Emotion	72.22 (58.33 to 86.11)	73.61 (58.33 to 88.89)		
SIS Participation	65.63 (40.63 to 90.63)	65.63 (40.63 to 90.63)		
SIS Recovery (VAS)	60.00 (40.00 to 80.00)	60.00 (40.00 to 80.00)		

Statistical analyses

Statistical analysis title	SIS Strength
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Statistical analysis description:

Comparison of fluoxetine vs Placebo - Mann Whitney test

Comparison groups	Placebo v Fluoxetine
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Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3844
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS Hand Ability at 12m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2813
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS mobility at 12m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5425
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS motor at 12m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3286
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS Daily activities at 12m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo

Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5808
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS Physical function at 12m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.372
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS Memory at 12m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4245
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS Communication at 12m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3138
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS emotion at 12m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo

Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7442
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS Participation at 12m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9295
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SIS Recovery (VAS) at 12m
Statistical analysis description:	
Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9333
Method	Wilcoxon (Mann-Whitney)

Secondary: Vitality Median (IQR)

End point title	Vitality Median (IQR)
End point description:	
Vitality Median (IQR)	
End point type	Secondary
End point timeframe:	
by 12m	

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1533	1528		
Units: units				
median (inter-quartile range (Q1-Q3))				
Vitality Median (IQR)	50.00 (37.50 to 75.00)	50.00 (37.50 to 75.00)		

Statistical analyses

Statistical analysis title	Validity Median (IQR) at 12m
Statistical analysis description: Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3061
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9043
Method	Wilcoxon (Mann-Whitney)

Secondary: Mental Health Inventory - 5 item at 12m

End point title	Mental Health Inventory - 5 item at 12m
End point description: Mental Health Inventory - 5 item at 12m	
End point type	Secondary
End point timeframe: by 12m	

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1530	1527		
Units: units				
median (inter-quartile range (Q1-Q3))				
MHI 5 Median (IQR)	72.00 (56.00 to 88.00)	76.00 (56.00 to 88.00)		

Statistical analyses

Statistical analysis title	MHI 5 (Median IQR) at 12m
Statistical analysis description: Comparison of fluoxetine vs Placebo - Mann Whitney test	
Comparison groups	Fluoxetine v Placebo

Number of subjects included in analysis	3057
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.711
Method	Wilcoxon (Mann-Whitney)

Secondary: Health related quality of life (EurQol - EQ5D-5L) at 12m excluding dead patients

End point title	Health related quality of life (EurQol - EQ5D-5L) at 12m excluding dead patients
End point description:	Health related quality of life (EurQol - EQ5D-5L) at 12m excluding dead patients
End point type	Secondary
End point timeframe:	by 12m

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1546	1550		
Units: units				
median (inter-quartile range (Q1-Q3))				
EQ5D-5L excluding dead patients	0.59 (0.24 to 0.75)	0.59 (0.27 to 0.77)		

Statistical analyses

Statistical analysis title	EQ5D-5L excluding dead patients
Statistical analysis description:	Comparison of fluoxetine vs Placebo - Mann Whitney test
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3096
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3091
Method	Wilcoxon (Mann-Whitney)

Secondary: Depression 12m

End point title	Depression 12m
End point description:	New Depression
End point type	Secondary

End point timeframe:
by 12m

End point values	Fluoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1564	1563		
Units: patients				
New Depression	292	327		
New Antidepressant	358	410		

Statistical analyses

Statistical analysis title	New Depression
Statistical analysis description: Comparison of fluoxetine vs Placebo - Chi squared	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1142
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.04
upper limit	0.54

Statistical analysis title	New Antidepressant
Statistical analysis description: Comparison of fluoxetine vs Placebo - Chi squared	
Comparison groups	Fluoxetine v Placebo
Number of subjects included in analysis	3127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.36
upper limit	-0.33

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

The trial systematically collected data on adverse events which may theoretically be associated with the IMP and the condition under investigation from randomisation to end of follow-up at 12 months.

Adverse event reporting additional description:

Recruiting hospitals identified and reported adverse events at discharge or death and readmission to hospital. Central coordinating centre staff followed up patients at 6 months and 12 months to measure the primary and secondary outcomes. Data on adverse events were also collected from participants GP's at 6 and 12 months.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Fluoxetine
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Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Our trial protocol specifically did not require any Adverse events to be reported unless they were serious, or fulfilled our definition of an outcome

Serious adverse events	Placebo	Fluoxetine	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 1563 (0.58%)	5 / 1564 (0.32%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
all neoplasms			
subjects affected / exposed	1 / 1563 (0.06%)	0 / 1564 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
all vascular disorders			
subjects affected / exposed	1 / 1563 (0.06%)	0 / 1564 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
All surgical and medical procedures			

subjects affected / exposed	4 / 1563 (0.26%)	3 / 1564 (0.19%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
All General disorders and administration site conditions			
subjects affected / exposed	3 / 1563 (0.19%)	1 / 1564 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Social circumstances			
all social circumstances			
subjects affected / exposed	1 / 1563 (0.06%)	0 / 1564 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
all respiratory and mediastinal disorders			
subjects affected / exposed	1 / 1563 (0.06%)	0 / 1564 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
all investigations			
subjects affected / exposed	2 / 1563 (0.13%)	3 / 1564 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
All cardiac disorders			
subjects affected / exposed	1 / 1563 (0.06%)	2 / 1564 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
All nervous system disorders			
subjects affected / exposed	2 / 1563 (0.13%)	3 / 1564 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

all blood disorders			
subjects affected / exposed	1 / 1563 (0.06%)	0 / 1564 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
All gastrointestinal disorders			
subjects affected / exposed	4 / 1563 (0.26%)	0 / 1564 (0.00%)	
occurrences causally related to treatment / all	1 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
all Hepatobiliary disorders			
subjects affected / exposed	2 / 1563 (0.13%)	0 / 1564 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
all renal and urinary disorders			
subjects affected / exposed	0 / 1563 (0.00%)	1 / 1564 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
all musculoskeletal			
subjects affected / exposed	0 / 1563 (0.00%)	1 / 1564 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
all metabolism disorders			
subjects affected / exposed	0 / 1563 (0.00%)	3 / 1564 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Fluoxetine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1563 (0.00%)	0 / 1564 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2012	<p>Description of amendments to V2 of the FOCUS trial protocol</p> <p>Substantial amendment 1: Section 10.3 Removal of the second mailing of patient questionnaires at 1, 6 and 12 months and change to telephone.</p> <p>Substantial amendment 2: Section 12.5.2 Removal of neuroleptic malignant syndrome-like events; anaphylactoid reactions; serotonin Syndrome; pancytopenia, thrombocytopenia or haemolytic anaemia from the list of adverse reactions which will be collected systematically on the discharge form and follow ups. Will be considered as AEs and reported according to our pharmacovigilance procedures which are unchanged.</p> <p>Substantial amendment 3: Timelines (page 47) Change to the expected start date from April 2012 to July 2012 due to delays in receiving the IMP.</p> <p>Substantial amendment 4: Section 14.4 Data Monitoring Committee. Clarification of the arrangements for sharing data with other parallel trials which will be based on the discretion of the Chair of our DMC.</p> <p>Substantial Amendment 5 Traditional PIB for Proxies V1 110512 was reworded to reflect that it is being read by the proxy rather than the patients.</p> <p>Substantial amendment 6 Removal of Protocol Appendix 1 which was replaced by a link.</p>

01 September 2015	<p>The original CTA was submitted prior to the final supplier of trial IMP being confirmed. Therefore the details of the MA holder which we originally submitted was not the MA holder of the IMP that we are now using (ATC code N06A B03). this amendment provided the correct MA details for the Oxactin 20mg we are using and ensures consistency with the details provided in our annual DSUR reports.</p> <p>Amendments: Change of MA holder and MA number details to reflect the specific IMP used for the trial Change in the response to question D2-2 in the CTA from 'yes' to 'no' as the same IMP has been used for each patient.</p> <p>Additional clerical amendments made: Section A4: Update to the ISRCTN number (this was not available at the time of the original submission). Section B1: Amendment to sponsor contact Section C1-5: Update to sponsor responsibility for sign off of CTA Section G4: Update to Network name and contact details Section H2-2: Date of ethics submission added as the original CTA was submitted prior to approval given. Section H2-3: Status changed to 'approved' and date of ethical approval added as the original CTA was submitted prior to approval given.</p> <p>Protocol amendments relating to the IMP Section 1.1 Background: Updated the link address to current SmPC Section 9.1 Study Drug: Updated IMP details Section 9.1.1 MA number: Updated MA number Section 9.1.3 MA holder: Updated MA holder details Section 9.4 Storage: Storage temperature updated Section 9.5 Management: Storage temperature updated</p> <p>Notification of change of funder from the 1st October 2014 for the main phase to the NIHR HTA.</p>
15 April 2016	Change of Chief Investigator.

21 November 2016	<p>This amendment was required following notification to the sponsor of a revision of the summary of Product characteristics for Oxactin 20mg PL 19611/0017 on 24th July 2015.</p> <p>The SmPC was revised as a result of a variation to the marketing authorisation to update the safety information in line with the Core Safety Profile which was issued following conclusion of Periodic Safety Update Report (PSUR) work sharing procedure FR/H/PSUR/0069/001. In addition, the SmPC was updated to align with the layout and headings in the current Quality Review of Documents (QRD) templates, including the standard statements now required to encourage reporting of suspected adverse reactions.</p> <p>Information included in the latest version of the SmPC contra-indicates the combined use of metoprolol for heart failure and fluoxetine. Following discussion with the trial sponsor it was agreed that immediate action could be implemented to ensure that any patients taking metoprolol for heart failure were excluded with immediate effect.</p> <p>Urgent Safety Measures taken to ensure patient safety: A change was made to the database on 16/11/16 to add metoprolol for heart failure to our current list of excluded medications with immediate effect. All contacts at each site were emailed to inform them of the immediate change to the exclusion criteria and a revised paper randomisation form provided for use with immediate effect. A database report was created for patients randomised who were taking metoprolol at the time of randomisation and who would still be taking the trial medication. Only five patients were affected and each one was checked by the Chief Investigator as to the indication for metoprolol and none were found to be taking the drug for heart failure 17th The MHRA were contacted to advise them of action taken on November and 21st it was confirmed as an urgent safety measure on November 2016. The Data Monitoring Committee and Steering Committee informed.</p> <p>.</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30528472>