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MS-SMART: MS-Secondary Progressive Multi-Arm Randomisation Trial

Submission date	Recruitment status	[X] Prospectively registered
25/10/2013	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
25/10/2013	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
28/05/2020	Nervous System Diseases	

Plain English summary of protocol

Background and study aims
Multiple sclerosis (MS) is a disabling and progressive neurological disease that affects about 100,000 people in the UK. Many patients with MS experience two phases of disease: early MS (also called relapsing remitting MS, RRMS) and late MS (also called secondary progressive MS or SPMS). Early MS is due to inflammation of the nerves and the insulation (called myelin) that surrounds the nerves. Early MS is often characterised by periods of 'attacks' interspersed with periods of 'remission' with no or low disease symptoms. Late or progressive MS, which affects the majority of patients and typically emerges after 10-15 years of disease, results from actual nerve death (also called neurodegeneration). The progressive stage of disease results not in individual attacks but slow, cumulative and irreversible disability affecting walking, balance, vision, cognition, pain control, bladder and bowel function. Critically, and unlike early disease, there is no proven treatment for the late stage of MS. This is therefore an urgent and major unmet health need. This study directly addresses this need and will evaluate three drugs (fluoxetine, riluzole and amiloride), all of which have shown some promise in MS, and in particular in SPMS.

Who can participate?
Men or women aged 25 to 65 with a confirmed diagnosis of SPMS

What does the study involve?
Patients will be randomly allocated to receive one of the three active drugs (fluoxetine, riluzole and amiloride) or an inactive placebo (dummy). All patients will have periodic magnetic resonance imaging (MRI) brain scans and after 96 weeks these will be analysed. We will then compare the scans to see if any of the drugs slow the rate of brain shrinkage that normally occurs in SPMS.

What are the possible benefits and risks of participating?
Not provided.

Where is the study run from?
Edinburgh Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
April 2013 to June 2018

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Miss Moira Ross
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(updated 19/07/2019, previously: moira.ross@ed.ac.uk)

Study website
http://www.ms-smart.org/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2012-005394-31

IRAS number

ClinicalTrials.gov number
NCT01910259

Secondary identifying numbers
15211

Study information

Scientific Title
MS-SMART: A Multi-Arm Phase IIb Randomised, Double Blind Placebo-Controlled Clinical Trial Comparing The Efficacy of 3 Neuroprotective Drugs in Secondary Progressive Multiple Sclerosis

Acronym
MS-SMART

Study objectives
The general aim is to determine the efficacy, and advance our understanding of the mechanism of action, of three putative neuroprotective repurposed drugs (fluoxetine, riluzole and amiloride) versus placebo, through MRI, disability measurement, OCT and targeted CSF analysis.

Hypothesis:
Drugs that target key neurodegeneration-causing pathways in MS will be neuroprotective as demonstrated by slowing the rate of brain volume loss in people with SPMS.

Aims:
Primary: to test against placebo, the efficacy of fluoxetine, riluzole and amiloride in SPMS over a two year period.

Secondary: to advance our understanding of the mechanisms of efficacy, noting that each drug targets distinct and key disease related mechanistic pathways.

Multiple sclerosis is the commonest disabling neurological disease affecting young adults in temperate latitudes. It is a progressive disorder of the brain and spinal cord. Many patients with MS experience two phases of disease: (i) early MS (relapsing remitting MS) and (ii) late MS, secondary progressive MS (SPMS), affecting the majority of patients after 10-15 years. SPMS results from nerve death that causes accumulating and irreversible disability. There is no proven treatment for SPMS and it is a major unmet health need for the NHS. These patients require

nerve protection treatments that will slow, stop and ultimately reverse progressive disease. A systematic review of all relevant pre-clinical and clinical data by the MS Clinical Trials Network and an international MS expert workshop led to the identification of three leading drugs (fluoxetine, riluzole or amiloride) suitable to trial in SPMS. The MS-SMART trial will test these drugs in 440 SPMS patients using a simultaneous multi-arm trial design, each compared against a dummy drug (placebo). Patients will be on the trial for up to week 100 (approximately 25 months) and will be recruited from specialist centres within the UK. Patients and treating trial clinician will not know which drug they are receiving to enable an unbiased testing of the drugs. All patients will have MRI (magnetic resonance imaging) brain scans and after 96 weeks these will be analysed to determine which drugs are the most promising. The main (primary) outcome is change in MRI, to see if any of the drugs can slow the rate of brain shrinkage that we would normally see in SPMS, supported by lesion and disability changes, compared to being on the dummy drug. This trial is a world-first in MS, with great economies of scale.

More details can be found at: http://www.nets.nihr.ac.uk/projects/eme/113011
Protocol can be found at: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0017/81152/PRO-11-30-11.pdf

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scotland A Research Ethics Committee, 28/01/2013, 13/SS/0007

Study design
Interventional multi-centre multi-arm phase IIB randomised double-blind placebo controlled clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Topic: Neurological; Subtopic: Neurological (all Subtopics); Disease: Nervous system disorders

Interventions
440 patients will be randomised equally (1:1:1:1) between the three active treatments and placebo to give 110 per treatment arm. The primary analysis will be intention-to-treat (ITT) on the whole study cohort (n=110/arm). Based on two UK phase II trials (Lamotrigine and MS-STAT),

we expect 10% of the total cohort to drop out of the trial before Year 2, a further 10% of the total cohort to come for their Year 2 visit, but be off medication. We anticipate 90 patients per arm completing the study.

1. Amiloride, 5 mg twice per day for 96 weeks (5 mg once per day for first 4 weeks)
2. Fluoxetine, 50 mg twice per day for 96 weeks (50 mg once per day for first 4 weeks)
3. Placebo, matched placebo for 96 weeks
4. Riluzole, 50 mg twice per day for 96 weeks (50 mg once per day for first 4 weeks)

Follow Up Length: 1 month
Study Entry: Registration and One or More Randomisations

Intervention Type
Other

Phase
Phase II

Primary outcome measure
MRI-derived Percentage Brain Volume Change (PBVC); Timepoint(s): Baseline, 96 weeks

Secondary outcome measures
MRI:
Count of new and enlarging T2 lesions

Pseudoatrophy:
To specifically examine for this, a baseline scan will be acquired 24 weeks after the start of treatment.

Clinical:
1. Expanded Disability Status Scale (EDSS)
2. Timed 25 Foot Walk (T25FW)
3. 9 Hole Peg Test (9HPT)
4. Paced Auditory Serial Addition Test (PASAT)
5. MS Functional Composite score comprising of the following:
5.1. Timed 25 Foot Walk (T25FW)
5.2. 9 Hole Peg Test (9HPT)
5.3. Paced Auditory Serial Addition Test (PASAT)
6. Symbol Digit Modalities Test (SDMT)
7. Sloan Low contrast visual acuity (SLCVA)
8. Relapse rate
9. Multiple Sclerosis Impact Scale v2 (MSIS29v2)
10. Multiple Sclerosis Walking Scale v2 (MSWSv2)
11. Brief Pain Inventory (BPI)
12. Numerical Pain Rating Score (NPRS)
13. Neurological Fatigue Index (NFI)
14. Health economics (EQ-5D)

Exploratory Mechanistic Endpoints

MRI:
1. Proportion of new T2 lesions at 24 weeks being persistently T1 hypointense at 96 weeks
2. Change in brain grey matter volume
3. MR spectroscopy (MRS)
4. MR magnetisation transfer ratio (MTR)
5. Cervical cord imaging

CSF: measurement of CSF neurofilament levels.

OCT: measurement of retinal nerve fibre layer (RNFL) and retinal nerve ganglion cell and inner plexiform layer (RGC+IPL).

Overall study start date
01/04/2013

Completion date
04/07/2018

Eligibility

Key inclusion criteria
Current inclusion criteria as of 24/05/2016:
1. Confirmed diagnosis of SPMS. Steady progression rather than relapse must be the major cause of increasing disability in the preceding 2 years. Progression can be evident from either an increase of at least one point in EDSS or clinical documentation of increasing disability in patients notes
2. EDSS 4.0-6.5
3. Aged 25 to 65 inclusive
4. Women and men with partners of childbearing potential must be using an appropriate method of contraception to avoid any unlikely teratogenic effects of the 3 drugs from time of consent, to 6 weeks after treatment inclusive
5. Women must have a negative pregnancy test within 7 days prior to the baseline visit unless not of child bearing potential (e.g. have undergone a hysterectomy, bilateral tubal ligation or bilateral oophorectomy or they are postmenopausal)
6. Willing and able to comply with the trial protocol (e.g. can tolerate MRI and fulfils the requirements for MRI, e.g. not fitted with pacemakers or permanent hearing aids) ability to understand and complete questionnaires
7. Written informed consent

Previous inclusion criteria:
1. Confirmed diagnosis of SPMS at randomisation
2. Steady progression rather than relapse must be the major cause of increasing disability in the preceding 2 years. Progression can be evident from either an increase of at least one point in EDSS or clinical documentation of increasing disability
3. EDSS 4.0-6.5
4. Aged 25 to 65
5. Men or Women of childbearing age must be using an appropriate method of contraception to avoid any unlikely teratogenic effects of the 3 drugs from time of consent and 6 weeks after treatment
6. Females have a negative pregnancy test within 7 days prior to being enrolled (baseline visit) unless not of child bearing potential eg have undergone a hysterectomy, bilateral tubal ligation

or bilateral oophorectomy or they are postmenopausal
7. Willing and able to comply with the trial protocol and have the ability to understand and complete questionnaires
8. Willing and able to give full written informed consent
9. Able to undertake MRI

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
UK Sample Size: 440

Total final enrolment
445

Key exclusion criteria
Current exclusion criteria as of 24/05/2016:
1. Pregnancy or breast feeding females
2. Baseline MRI scan not of adequate quality for analysis (e.g. too much movement artefact)
3. Significant organ co-morbidity (e.g. malignancy or renal or hepatic failure)
4. Relapse within 3 months of baseline visit
5. Patients who have been treated with iv or oral steroids for an MS relapse/progression within 3 months of baseline visit (these patients can undergo future screening visits once the 3 month window has expired) , patients on steroids for another medical condition may enter as long as the steroid prescription is not for multiple sclerosis (relapse/ progression)
6. Use of Simvastatin at 80mg dose within 3 months of baseline visit (lower doses of Simvastatin and other statins are permissible)
7. Commencement of fampridine within 6 months of baseline visit
8. Use of immunosupressants (e.g. azathioprine, methotrexate, cyclosporine) or first generation disease modifying treatments (β-interferons, glatiramer) within 6 months of baseline visit
9. Use of fingolimod/fumarate/teriflunomide/laquinomod/or other experimental disease modifying treatment (including research in an investigational medicinal product) within 12 months of baseline visit
10. Use of mitoxantrone/natalizumab/alemtuzumab/daclizumab if treated within 12 months of baseline visit
11. Primary progressive MS
12. Relapsing-remitting MS
13. Known hypersensitivity to the active substances and their excipients to any of the active drugs for this trial
14. Use of an SSRI within 6 months of the baseline visit
15. Current use of tamoxifen
16. Current use of herbal treatments containing St. John’s Wort
17. Patients with a history of bleeding disorders or currently on anticoagulants
18. Use of monoamine oxidase inhibitors, phenytoin, L-tryptophan and/or neuroleptic drugs within 6 months of the baseline visit

19. Use of: lithium, chlorpropamide, triamterene, spironolactone, within 6 months of the baseline visit
20. Current use of potassium supplements
21. Significant signs of depression
22. Bipolar disorder
23. A Beck Depression Index score of 19 or higher
24. Epilepsy/seizures
25. Receiving or previously received Electroconvulsive therapy treatment
26. Glaucoma
27. Routine screening blood values (LFT) >/ 3 x upper limit of normal (ULN) of site reference ranges (AST/ALT, bilirubin, GT)
28. Potassium <2.8mmol/l or >5.5mmol/l
29. Sodium <125mmol/l
30. Creatinine >130µmol/l
31. WBCs <3x109/l
32. Lymphocytes <0.8 x 109/l
33. Neutrophil count <1.0 x109 /l
34. Platelet count <90 x109 /l
35. Haemoglobin <80g/l

Previous exclusion criteria:
1. Pregnancy or breast feeding females
2. Patients unable to tolerate baseline MRI scan or scan not of adequate quality for analysis (eg too much movement artefact)
3. Patients fitted with pacemakers or permanent hearing aids
4. Significant organ comorbidity (eg malignancy or renal or hepatic failure)
5. Routine screening blood values (LFT) >/ 3 x upper limit of normal (ULN) of site reference ranges (ALT, bilirubin, SGT)
6. Potassium >5.5mmol/l
7. Sodium <125mmol/l
8. Creatinine >130µmol/l
9. Total white cell count <2.0 x109 /l
10. Neutrophil count <1.0 x109 /l
11. Platelet count <100 x109 /l
12. Haemoglobin <8.0g/l
13. Relapse within 3 months of baseline visit
14. Patients who have been treated with iv or oral steroids within 3 months of baseline visit (these patients can undergo future screening visits once the 3 month window has expired)
15. Commencement of Fampridine within 6 months of baseline visit
16. Use of immunosupressants (eg azathioprine, methotrexate, cyclosporine) or first generation disease modifying
treatments (ß-interferons, glatiramer) within 6 months of baseline visit
17. Use of fingolimod/fumarate/teriflunomide/laquinomod/or other experimental disease modifying treatment (including research in an investigational medicinal product) within 12 months of baseline visit
18. Use of mitoxantrone/natalizumab/alemtuzumab/daclizumab if treated within 12 months of baseline visit
19. Primary progressive MS
20. Relapsing-remitting MS
21. Known hypersensitivity to the active substances and their excipients to any of the active

drugs for this trial
22. Use of: lithium, chlorpropamide, triamterene, spironolactone,
23. Use of potassium supplements

Date of first enrolment
18/12/2014

Date of final enrolment
22/06/2016

Locations

Countries of recruitment
Scotland

United Kingdom

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Edinburgh Clinical Trials Unit
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Sponsor type
University/education

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ROR

https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
Efficacy and Mechanism Evaluation Programme

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, EME

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
To be confirmed at a later date

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	30/08/2018	10/04/2019	Yes	No
Basic results			28/05/2020	No	No
HRA research summary			28/06/2023	No	No