Clinical trial results:
High-field structural and functional MRI to investigate the substrates of fatigue in multiple sclerosis and to monitor the effect of tailored treatments.Pharmacological substudy.

Summary

EudraCT number	2010-023678-38
Trial protocol	IT
Global end of trial date	03 September 2014

Results information

Result version number	v1
This version publication date	23 February 2020
First version publication date	23 February 2020
Summary attachment (see zip file)	Eudract-2010-023678-38-summary (EUDRA-CT-2010-023678-38-summary.doc)

Trial information

Trial identification

Sponsor protocol code	GR-2008-1138784 sottostudio

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	IRCCS San Raffaele Scientific Institute
Sponsor organisation address	via Olgettina 60, Milan, Italy, 20132
Public contact	Prof. Massimo Filippi, IRCCS San Raffaele Scientific Institute, +39 0226433054, filippi.massimo@hsr.it
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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	03 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 September 2014
Global end of trial reached?	Yes
Global end of trial date	03 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main aim of this trial was to evaluate the effects on brain activation patterns of drugs that are widely used in clinical practice for the treatment of fatigue in multiple sclerosis

Protection of trial subjects:

Patients were monitored by a medical doctor during the entire experimental procedure, including MRI assessment. Medical advice was provided to patients about possible pharmacological treatments to solve eventual side effects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 June 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	45
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with multiple sclerosis (MS) and the relapsing-remitting (RR) or secondary progressive (SP) disease phenotype were recruited. Patients had to suffer from central fatigue at least from six weeks. Fatigue was assessed using proper evaluation scales, such as the modified fatigue impact scale (MFIS).

Pre-assignment

Screening details:

Inclusion/exclusion criteria: no relapses/steroid treatment <3 months before study; EDSS score<=4.0; no visual deficits; no right upper limb impairment interfering with fMRI; no other major neurological/psychiatric/mood disorders; no major renal/cardiac/hepatic diseases; no depression; no history of drug/alcohol abuse; no pregnancy/breastfeeding

Period 1

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

Blinding implementation details:

Blinding was performed using a computerized procedure

Arms

Are arms mutually exclusive?	Yes
Arm title	Fampridine

Arm description:

Fampridine treatment group (4-aminopyridine)

Arm type	Experimental
Investigational medicinal product name	Fampridine
Investigational medicinal product code	
Other name	Ampyra
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg twice daily (8:00 and 20:00 h)

Arm title	Amantadine

Arm description:

Amantadine treatment group (1-adamantylamine)

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

Dosage and administration details:

100 mg twice daily (8:00 and 20:00 h)

Arm title	Placebo

Arm description:

Placebo group

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet twice daily (8:00 and 20:00 h)

Number of subjects in period 1	Fampridine	Amantadine	Placebo
Started	15	15	15
Completed	14	15	15
Not completed	1	0	0
Adverse event, non-fatal	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Fampridine
Reporting group description:	
Fampridine treatment group (4-aminopyridine)	
Reporting group title	Amantadine
Reporting group description:	
Amantadine treatment group (1-adamantylamine)	
Reporting group title	Placebo
Reporting group description:	
Placebo group	

Reporting group values	Fampridine	Amantadine	Placebo
Number of subjects	15	15	15
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)	15	15	15
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	44.4	41.2	41.8
standard deviation	± 13.3	± 7.2	± 10.7
Gender categorical			
Units: Subjects			
Female	6	13	12
Male	9	2	3

Reporting group values	Total		
Number of subjects	45		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	45		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	31		
Male	14		

End points

End points reporting groups

Reporting group title	Fampridine
Reporting group description: Fampridine treatment group (4-aminopyridine)	
Reporting group title	Amantadine
Reporting group description: Amantadine treatment group (1-adamantylamine)	
Reporting group title	Placebo
Reporting group description: Placebo group	

Subject analysis set title	Fampridine baseline
Subject analysis set type	Full analysis
Subject analysis set description: Patients treated with fampridine - baseline	
Subject analysis set title	Fampridine week 4
Subject analysis set type	Full analysis
Subject analysis set description: Patients treated with fampridine - week 4	
Subject analysis set title	Amantadine baseline
Subject analysis set type	Full analysis
Subject analysis set description: Patients treated with amantadine - baseline	
Subject analysis set title	Amantadine week 4
Subject analysis set type	Full analysis
Subject analysis set description: Patients treated with amantadine - week 4	
Subject analysis set title	Placebo baseline
Subject analysis set type	Full analysis
Subject analysis set description: Patients taking placebo - baseline	
Subject analysis set title	Placebo week 4
Subject analysis set type	Full analysis
Subject analysis set description: Patients taking placebo - week 4	

Primary: Global MFIS

End point title	Global MFIS
End point description: modified fatigue impact scale, global score of fatigue	
End point type	Primary
End point timeframe: baseline and week 4	

End point values	Fampridine baseline	Fampridine week 4	Amantadine baseline	Amantadine week 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	15[1]	15
Units: unitless				
arithmetic mean (standard deviation)	45.1 (± 13.6)	34.3 (± 12.1)	46.3 (± 16.2)	34.4 (± 15.7)

Notes:

[1] - 1 miss

End point values	Placebo baseline	Placebo week 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15[2]		
Units: unitless				
arithmetic mean (standard deviation)	46.2 (± 12.8)	39.6 (± 13.5)		

Notes:

[2] - 1 miss

Statistical analyses

Statistical analysis title	within-group change global MFIS fampridine

Statistical analysis description:

change of global MFIS over time at week 4 vs baseline in fampridine group

Comparison groups	Fampridine baseline v Fampridine week 4
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.001
Method	t-test, 2-sided

Notes:

[3] - paired t test

Statistical analysis title	within-group change global MFIS amantadine

Statistical analysis description:

change of global MFIS over time at week 4 vs baseline in amantadine group

Comparison groups	Amantadine baseline v Amantadine week 4
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.023
Method	t-test, 2-sided

Notes:

[4] - paired t test

Statistical analysis title	within-group change global MFIS placebo

Statistical analysis description:

change of global MFIS over time at week 4 vs baseline in placebo group

Comparison groups	Placebo baseline v Placebo week 4

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.08
Method	t-test, 2-sided

Notes:
[5] - paired t test

Primary: Physical MFIS

End point title	Physical MFIS

End point description:
modified fatigue impact scale, score of physical fatigue

End point type	Primary

End point timeframe:
baseline and week 4

End point values	Fampridine baseline	Fampridine week 4	Amantadine baseline	Amantadine week 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	15[6]	15
Units: unitless				
arithmetic mean (standard deviation)	24.8 (± 7.0)	18.8 (± 6.7)	22.8 (± 7.3)	16.6 (± 7.5)

Notes:
[6] - 1 miss

End point values	Placebo baseline	Placebo week 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15[7]		
Units: unitless				
arithmetic mean (standard deviation)	20.8 (± 4.8)	16.8 (± 5.7)		

Notes:
[7] - 1 miss

Statistical analyses

Statistical analysis title	within-group change physical MFIS fampridine

Statistical analysis description:
change of physical MFIS over time at week 4 vs baseline in fampridine group

Comparison groups	Fampridine baseline v Fampridine week 4
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.003
Method	t-test, 2-sided

Notes:
[8] - paired t test

Statistical analysis title	within-group change physical MFIS amantadine
Statistical analysis description: change of physical MFIS over time at week 4 vs baseline in amantadine group	
Comparison groups	Amantadine baseline v Amantadine week 4
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.019
Method	t-test, 2-sided

Notes:
[9] - paired t test

Statistical analysis title	within-group change physical MFIS placebo
Statistical analysis description: change of physical MFIS over time at week 4 vs baseline in placebo group	
Comparison groups	Placebo baseline v Placebo week 4
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.043
Method	t-test, 2-sided

Notes:
[10] - paired t test

Primary: Cognitive MFIS	
End point title	Cognitive MFIS
End point description: modified fatigue impact scale, score of cognitive fatigue	
End point type	Primary
End point timeframe: baseline and week 4	

End point values	Fampridine baseline	Fampridine week 4	Amantadine baseline	Amantadine week 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	15[11]	15
Units: unitless				
arithmetic mean (standard deviation)	16.8 (± 9.0)	12.7 (± 7.8)	19.1 (± 9.4)	14.7 (± 9.5)

Notes:
[11] - 1 miss

End point values	Placebo baseline	Placebo week 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15[12]		
Units: unitless				
arithmetic mean (standard deviation)	20.9 (± 8.1)	19.3 (± 8.2)		

Notes:
[12] - 1 miss

Statistical analyses

Statistical analysis title	within-group change cognitive MFIS fampridine

Statistical analysis description:
change of cognitive MFIS over time at week 4 vs baseline in fampridine group

Comparison groups	Fampridine baseline v Fampridine week 4
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.014
Method	t-test, 2-sided

Notes:
[13] - paired t test

Statistical analysis title	within-group change cognitive MFIS amantadine

Statistical analysis description:
change of cognitive MFIS over time at week 4 vs baseline in amantadine group

Comparison groups	Amantadine baseline v Amantadine week 4
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.07
Method	t-test, 2-sided

Notes:
[14] - paired t test

Statistical analysis title	within-group change cognitive MFIS placebo

Statistical analysis description:
change of cognitive MFIS over time at week 4 vs baseline in placebo group

Comparison groups	Placebo baseline v Placebo week 4
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.32
Method	t-test, 2-sided

Notes:
[15] - paired t test

Primary: Psycho-social MFIS

End point title	Psycho-social MFIS

End point description:

End point type	Primary

End point timeframe:
baseline and week 4

End point values	Fampridine baseline	Fampridine week 4	Amantadine baseline	Amantadine week 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	15[16]	15
Units: unitless				
arithmetic mean (standard deviation)	3.5 (± 1.4)	2.8 (± 1.6)	4.3 (± 1.4)	3.1 (± 2.2)

Notes:
[16] - 1 miss

End point values	Placebo baseline	Placebo week 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15[17]		
Units: unitless				
arithmetic mean (standard deviation)	4.4 (± 1.4)	3.5 (± 1.3)		

Notes:
[17] - 1 miss

Statistical analyses

Statistical analysis title	within-group change psycho-social MFIS fampridine

Statistical analysis description:
change of psycho-social MFIS over time at week 4 vs baseline in fampridine group

Comparison groups	Fampridine baseline v Fampridine week 4
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.15
Method	t-test, 2-sided

Notes:
[18] - paired t test

Statistical analysis title	within-group change psycho-social MFIS amantadine

Statistical analysis description:
change of psycho-social MFIS over time at week 4 vs baseline in amantadine group

Comparison groups	Amantadine baseline v Amantadine week 4
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.023
Method	t-test, 2-sided

Notes:
[19] - paired t test

Statistical analysis title	within-group change psycho-social MFIS placebo
Statistical analysis description: change of psycho-social MFIS over time at week 4 vs baseline in placebo group	
Comparison groups	Placebo baseline v Placebo week 4
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.02
Method	t-test, 2-sided

Notes:
[20] - paired t test

Primary: motor fMRI activity	
End point title	motor fMRI activity
End point description: functional MRI activity during a right-hand motor task	
End point type	Primary
End point timeframe: baseline and week 4	

End point values	Fampridine baseline	Fampridine week 4	Amantadine baseline	Amantadine week 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	15	15
Units: BOLD signal				
number (not applicable)	15	14	15	15

End point values	Placebo baseline	Placebo week 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: BOLD signal				
number (not applicable)	15	15		

Statistical analyses

Statistical analysis title	within-group change motor fMRI activity fampridine
Statistical analysis description: change over time at week 4 vs baseline of motor fMRI activity in fampridine group	
Comparison groups	Fampridine baseline v Fampridine week 4

Number of subjects included in analysis	29
Analysis specification	Post-hoc
Analysis type	other[21]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[21] - voxel-wise paired t test using statistical parametric mapping (SPM12)

fmri changes localized in: left precentral gyrus (MNI space coordinates: -34 6 42), right superior frontal gyrus (MNI space coordinates: 18 38 48), left supramarginal gyrus (MNI space coordinates: -64 -22 28) and right supramarginal gyrus (MNI space coordinates: 58 10 28)

Statistical analysis title	within-group change motor fMRI activity placebo

Statistical analysis description:

change over time at week 4 vs baseline of motor fMRI activity in placebo group

Comparison groups	Placebo baseline v Placebo week 4
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	other[22]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[22] - voxel-wise paired t test using statistical parametric mapping (SPM12)

fMRI changes localized in the right middle temporal gyrus (MNI space coordinates: 58 10 28)

Primary: cognitive fMRI activity

End point title	cognitive fMRI activity

End point description:

functional MRI activity during a cognitive task - continuous performance test (CPT)

End point type	Primary

End point timeframe:

baseline and week 4

End point values	Fampridine baseline	Fampridine week 4	Amantadine baseline	Amantadine week 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15[23]	14	15	15
Units: BOLD signal				
number (not applicable)	15	14	15	15

Notes:

[23] - 15

End point values	Placebo baseline	Placebo week 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: BOLD signal				
number (not applicable)	15	15		

Statistical analyses

Statistical analysis title	within-group change CPT fMRI activity fampridine
Statistical analysis description: change over time at week 4 vs baseline of CPT fMRI activity in fampridine group	
Comparison groups	Fampridine baseline v Fampridine week 4
Number of subjects included in analysis	29
Analysis specification	Post-hoc
Analysis type	other[24]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[24] - voxel-wise paired t test using statistical parametric mapping (SPM12)

fMRI changes localized in: right cerebellum (MNI space coordinates: 22 -26 -24 and 12 -60 -26), left cerebellum (MNI space coordinates: -24 -58 -30), left MT/V5 (MNI space coordinates: -26 -74 16), right MT/V5 (MNI space coordinates: 34 -64 14) and left inferior parietal lobule (MNI space coordinates: -58 -28 50)

Statistical analysis title	within-group change CPT fMRI activity placebo
Statistical analysis description: change over time at week 4 vs baseline of CPT fMRI activity in placebo group	
Comparison groups	Placebo baseline v Placebo week 4
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	other[25]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[25] - voxel-wise paired t test using statistical parametric mapping (SPM12)

fMRI changes localized in: left precentral gyrus (MNI space coordinates: -36 6 36), left inferior frontal gyrus (MNI space coordinates: -46 32 10), left superior temporal gyrus (MNI space coordinates: -46 -42 16), right angular gyrus (MNI space coordinates: 42 -58 26), right supramarginal gyrus (MNI space coordinates: 52 -46 34) and left middle temporal gyrus (MNI space coordinates: -46 -24 0)

Primary: resting state functional connectivity default mode network

End point title	resting state functional connectivity default mode network
End point description: resting state functional connectivity in the default mode network	
End point type	Primary
End point timeframe: baseline and week 4	

End point values	Fampridine baseline	Fampridine week 4	Amantadine baseline	Amantadine week 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	15	15
Units: BOLD signal				
number (not applicable)	13	13	13	13

End point values	Placebo baseline	Placebo week 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: BOLD signal				
number (not applicable)	13	13		

Statistical analyses

Statistical analysis title	within-group change RS FC fampridine

Statistical analysis description:

change over time at week 4 vs baseline of resting state functional connectivity in the default mode network in fampridine group

Comparison groups	Fampridine baseline v Fampridine week 4
Number of subjects included in analysis	29
Analysis specification	Post-hoc
Analysis type	other[26]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[26] - voxel-wise paired t test using statistical parametric mapping (SPM12)

RS FC changes localized in the left precuneus (MNI space coordinates: -10 -86 32) and right precuneus (MNI space coordinates: 8 -66 52)

Primary: resting state functional connectivity salience network

End point title	resting state functional connectivity salience network

End point description:

resting state functional connectivity in the salience network

End point type	Primary

End point timeframe:

baseline and week 4

End point values	Fampridine baseline	Fampridine week 4	Amantadine baseline	Amantadine week 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	15	15
Units: BOLD signal				
number (not applicable)	13	13	13	13

End point values	Placebo baseline	Placebo week 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: BOLD signal				
number (not applicable)	13	13		

Statistical analyses

Statistical analysis title	within-group change RS FC fampridine

Statistical analysis description:

change over time at week 4 vs baseline of resting state functional connectivity in the salience network in fampridine group

Comparison groups	Fampridine baseline v Fampridine week 4
Number of subjects included in analysis	29
Analysis specification	Post-hoc
Analysis type	other[27]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[27] - voxel-wise paired t test using statistical parametric mapping (SPM12)

RS FC changes localized in the right inferior frontal gyrus (MNI space coordinates: 26 26 -12)

Primary: resting state functional connectivity fronto-parietal network

End point title	resting state functional connectivity fronto-parietal network

End point description:

resting state functional connectivity in the fronto-parietal network

End point type	Primary

End point timeframe:

baseline and week 4

End point values	Fampridine baseline	Fampridine week 4	Amantadine baseline	Amantadine week 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	15	15
Units: BOLD signal				
number (not applicable)	13	13	13	13

End point values	Placebo baseline	Placebo week 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: BOLD signal				
number (not applicable)	13	13		

Statistical analyses

Statistical analysis title	within-group change RS FC fampridine

Statistical analysis description:

change over time at week 4 vs baseline of resting state functional connectivity in the fronto-parietal network in fampridine group

Comparison groups	Fampridine baseline v Fampridine week 4
Number of subjects included in analysis	29
Analysis specification	Post-hoc
Analysis type	other[28]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[28] - voxel-wise paired t test using statistical parametric mapping (SPM12)

RS FC changes in the right inferior frontal gyrus (MNI space coordinates: 54 12 14)

Statistical analysis title	within-group change RS FC amantadine

Statistical analysis description:

change over time at week 4 vs baseline in the fronto-parietal network in amantadine group

Comparison groups	Amantadine baseline v Amantadine week 4
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	other[29]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[29] - voxel-wise paired t test using statistical parametric mapping (SPM12)

RS FC changes in the right superior parietal lobule (MNI space coordinates: 24 -66 40), right supplementary motor area (MNI space coordinates: 4 12 54), right middle frontal gyrus (MNI space coordinates: 44 32 24)

Statistical analysis title	within-group change RS FC placebo

Statistical analysis description:

change over time at week 4 vs baseline of resting state functional connectivity in the fronto-parietal network in placebo group

Comparison groups	Placebo baseline v Placebo week 4

Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	other[30]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[30] - voxel-wise paired t test using statistical parametric mapping (SPM12)

RS FC changes in the left angular gyrus (MNI space coordinates: -38 -60 42) and left middle temporal gyrus (MNI space coordinates: -62 -32 6)

Primary: resting state functional connectivity sensorimotor network

End point title	resting state functional connectivity sensorimotor network

End point description:

resting state functional connectivity in the sensorimotor network

End point type	Primary

End point timeframe:

baseline and week 4

End point values	Fampridine baseline	Fampridine week 4	Amantadine baseline	Amantadine week 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	15	15
Units: BOLD signal				
number (not applicable)	13	13	13	13

End point values	Placebo baseline	Placebo week 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: BOLD signal				
number (not applicable)	13	13		

Statistical analyses

Statistical analysis title	within-group change RS FC fampridine

Statistical analysis description:

change over time at week 4 vs baseline of resting state functional connectivity in the sensorimotor network in fampridine group

Comparison groups	Fampridine baseline v Fampridine week 4

Number of subjects included in analysis	29
Analysis specification	Post-hoc
Analysis type	other[31]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[31] - voxel-wise paired t test using statistical parametric mapping (SPM12)

RS FC changes localized in the right cerebellum (MNI space coordinates: 18 -50 -22) and right postcentral gyrus (MNI space coordinates: 30 -30 50)

Statistical analysis title	within-group change RS FC amantadine

Statistical analysis description:

change over time at week 4 vs baseline of resting state functional connectivity in the sensorimotor network in amantadine group

Comparison groups	Amantadine baseline v Amantadine week 4
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	other[32]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[32] - voxel-wise paired t test using statistical parametric mapping (SPM12)

RS FC changes localized in the right supplementary motor area (MNI space coordinates: 14 -26 52) and left secondary somatosensory cortex (MNI space coordinates: -56 -18 18)

Statistical analysis title	within-group change RS FC placebo

Statistical analysis description:

within-group change of resting state functional connectivity in the sensorimotor network in placebo group

Comparison groups	Placebo baseline v Placebo week 4
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	other[33]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[33] - voxel-wise paired t test using statistical parametric mapping (SPM12)

RS FC changes localized in the right postcentral gyrus (MNI space coordinates: 46 -22 40) and right paracentral lobule (MNI space coordinates: 10 -36 52)

Primary: resting state functional connectivity basal ganglia network

End point title	resting state functional connectivity basal ganglia network

End point description:

resting state functional connectivity in the basal ganglia network

End point type	Primary

End point timeframe:

baseline and week 4

End point values	Fampridine baseline	Fampridine week 4	Amantadine baseline	Amantadine week 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	14	15	15
Units: BOLD signal				
number (not applicable)	13	13	13	13

End point values	Placebo baseline	Placebo week 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: BOLD signal				
number (not applicable)	13	13		

Statistical analyses

Statistical analysis title	within-group change RS FC fampridine

Statistical analysis description:

change over time at week 4 vs baseline of resting state functional connectivity in the basal ganglia network in fampridine group

Comparison groups	Fampridine week 4 v Fampridine baseline
Number of subjects included in analysis	29
Analysis specification	Post-hoc
Analysis type	other[34]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[34] - voxel-wise paired t test using statistical parametric mapping (SPM12)

RS FC changes localized in the left caudate nucleus/putamen (MNI space coordinates: -24 -10 4)

Statistical analysis title	within-group change RS FC placebo

Statistical analysis description:

change over time at week 4 vs baseline of resting state functional connectivity in the basal ganglia network in placebo group

Comparison groups	Placebo baseline v Placebo week 4
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	other[35]
P-value	< 0.001
Method	t-test, 2-sided

Notes:

[35] - voxel-wise paired t testv using statistical parametric mapping (SPM12)

RS FC changes localized in the left thalamus (MNI space coordinates: -10 -4 12)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: July 2011-February 2014	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19
Reporting groups	
Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 45 (13.33%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Paresthesia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Dysesthesia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
General disorders and administration site conditions			

Insomnia subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2		
Ear and labyrinth disorders Gait disturbance subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Pyrosis subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1 1 / 45 (2.22%) 1		
Respiratory, thoracic and mediastinal disorders Sinusitis subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported