



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 |
| Scientific contact | Prof. Massimo Filippi, IRCCS San Raffaele Scientific Institute, +39 0226433054, filippi.massimo@hsr.it |

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 (\pm 1.4) | 2.8 (\pm 1.6) | 4.3 (\pm 1.4) | 3.1 (\pm 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 (\pm 1.4) | 3.5 (\pm 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