# Clinical trial results:
# A 6-month, multicenter, randomized, controlled parallel group study to evaluate the effect of physical training on fatigue in patients with relapsing-remitting multiple sclerosis treated with fingolimod, followed by a 6 month optional extension phase

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

| | |
|---|---|
| EudraCT number | 2011-002969-38 |
| Trial protocol | DE |
| Global end of trial date | 14 July 2014 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 08 July 2016 |
| First version publication date | 13 August 2015 |
| Version creation reason | |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | CFTY720DDE07 |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 x, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 x, |

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 | 14 July 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 July 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 July 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of structured physical e-training vs. no training on fatigue in Gilenya®-treated RRMS patients after 6 months; assessed by the modified fatigue impact scale (mFIS).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 24 November 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 | Germany: 178 |
| Worldwide total number of subjects | 178 |
| EEA total number of subjects | 178 |

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) | 178 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were randomized1:1 to receive a structured physical intervention (e-training) or no physical intervention (waiting).

### Pre-assignment

Screening details:

At the end of the 6 month core phase (phase 1), participants in the waiting group had the option to receive e-training for 6 months in the phase 2 optional extension. Participants in the e-training group had the option to continue their e-training for another 6 months in the phase 2 extension.

### Period 1

| | |
|---|---|
| Period 1 title | Phase 1 |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | E-training |

Arm description:

Fingolimod as baseline immunomodulatory multiple sclerosis treatment was prescribed as per clinical practice. During phase 1, participants randomized to this arm had an introductory group session, hosted by a sports therapist. The individual training schedule was comprised of strength exercises twice a week for 30-45 minutes and endurance training once a week for 20-60 minutes for 6 months. The participants documented each training session thoroughly via the web-based application (duration, type of exercises, number of repetitions and sets, perceived exertion). A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses as clinically warranted. Steroid treatment consisted of 3-5 days and up to 1,000 mg methylprednisolone/day. After 6 months, Phase 2, the same Phase 1 regimen applied.

| | |
|---|---|
| Arm type | Physical exercise with fingolimod |
| Investigational medicinal product name | no investigational product |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

no investigational treatment was administered; fingolimod administered according to local practice

| | |
|---|---|
| **Arm title** | Waiting |

Arm description:

Fingolimod as baseline immunomodulatory multiple sclerosis treatment is prescribed as per clinical practice. During Phase 1, participants randomized to this arm did not receive e-training exercise. After a 6 month waiting period, phase 2, participants had an introductory group session, hosted by a sports therapist. The individual training schedule was comprised of strength exercises twice a week for 30-45 minutes and endurance training once a week for 20-60 minutes for 6 months. The participants documented each training session thoroughly via the web-based application (duration, type of exercises, number of repetitions and sets, perceived exertion). A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses as clinically warranted. Steroid treatment consisted of 3-5 days and up to 1,000 mg methylprednisolone/day.

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| Number of subjects in period 1 | E-training | Waiting |
|---|---|---|
| Started | 94 | 84 |
| Modified Full Analysis Set | 56 [1] | 83 |
| Completed | 84 | 78 |
| Not completed | 10 | 6 |
| Consent withdrawn by subject | 6 | 5 |
| Visit 6a omitted | 1 | - |
| Adverse event, non-fatal | 2 | 1 |
| Lost to follow-up | 1 | - |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: A modified analysis set, consisting of patients who had sufficient e-training compliance, was used for the analysis.

## Period 2

| | |
|---|---|
| Period 2 title | Phase 2 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | E-training |

Arm description:

Fingolimod as baseline immunomodulatory multiple sclerosis treatment was prescribed as per clinical practice. During phase 1, participants randomized to this arm had an introductory group session, hosted by a sports therapist. The individual training schedule was comprised of strength exercises twice a week for 30-45 minutes and endurance training once a week for 20-60 minutes for 6 months. The participants documented each training session thoroughly via the web-based application (duration, type of exercises, number of repetitions and sets, perceived exertion). A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses as clinically warranted. Steroid treatment consisted of 3-5 days and up to 1,000 mg methylprednisolone/day. After 6 months, Phase 2, the same Phase 1 regimen applied.

| | |
|---|---|
| Arm type | Physical exercise with fingolimod |

No investigational medicinal product assigned in this arm

| | |
|---|---|
| **Arm title** | Waiting |

Arm description:

Fingolimod as baseline immunomodulatory multiple sclerosis treatment is prescribed as per clinical practice. During Phase 1, participants randomized to this arm did not receive e-training exercise. After a 6 month waiting period, phase 2, participants had an introductory group session, hosted by a sports therapist. The individual training schedule was comprised of strength exercises twice a week for 30-45 minutes and endurance training once a week for 20-60 minutes for 6 months. The participants documented each training session thoroughly via the web-based application (duration, type of exercises, number of repetitions and sets, perceived exertion). A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses as clinically warranted. Steroid treatment consisted of 3-5 days and up to 1,000 mg methylprednisolone/day.

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| **Number of subjects in period 2[2]** | E-training | Waiting |
|---|---|---|
| Started | 81 | 74 |
| Completed | 75 | 68 |
| Not completed | 6 | 6 |
| Consent withdrawn by subject | 4 | 3 |
| Adverse event, non-fatal | 1 | 1 |
| Lost to follow-up | 1 | 1 |
| Permanent interruption of fingolimod | - | 1 |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Every patient who completed Phase 1 did not enter Phase 2.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | E-training |

Reporting group description:

Fingolimod as baseline immunomodulatory multiple sclerosis treatment was prescribed as per clinical practice. During phase 1, participants randomized to this arm had an introductory group session, hosted by a sports therapist. The individual training schedule was comprised of strength exercises twice a week for 30-45 minutes and endurance training once a week for 20-60 minutes for 6 months. The participants documented each training session thoroughly via the web-based application (duration, type of exercises, number of repetitions and sets, perceived exertion). A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses as clinically warranted. Steroid treatment consisted of 3-5 days and up to 1,000 mg methylprednisolone/day. After 6 months, Phase 2, the same Phase 1 regimen applied.

| Reporting group title | Waiting |
|---|---|

Reporting group description:

Fingolimod as baseline immunomodulatory multiple sclerosis treatment is prescribed as per clinical practice. During Phase 1, participants randomized to this arm did not receive e-training exercise. After a 6 month waiting period, phase 2, participants had an introductory group session, hosted by a sports therapist. The individual training schedule was comprised of strength exercises twice a week for 30-45 minutes and endurance training once a week for 20-60 minutes for 6 months. The participants documented each training session thoroughly via the web-based application (duration, type of exercises, number of repetitions and sets, perceived exertion). A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses as clinically warranted. Steroid treatment consisted of 3-5 days and up to 1,000 mg methylprednisolone/day.

| Reporting group values | E-training | Waiting | Total |
|---|---|---|---|
| Number of subjects | 94 | 84 | 178 |
| Age categorical<br>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) | 94 | 84 | 178 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous \|<br>Units: Years | | | |
| arithmetic mean | 40.9 | 39.4 | |
| standard deviation | ± 10.4 | ± 8.7 | - |
| Gender, Male/Female<br>Units: Participants | | | |
| Female | 65 | 57 | 122 |
| Male | 29 | 27 | 56 |

## End points

### End points reporting groups

| Reporting group title | E-training |
|---|---|

Reporting group description:

Fingolimod as baseline immunomodulatory multiple sclerosis treatment was prescribed as per clinical practice. During phase 1, participants randomized to this arm had an introductory group session, hosted by a sports therapist. The individual training schedule was comprised of strength exercises twice a week for 30-45 minutes and endurance training once a week for 20-60 minutes for 6 months. The participants documented each training session thoroughly via the web-based application (duration, type of exercises, number of repetitions and sets, perceived exertion). A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses as clinically warranted. Steroid treatment consisted of 3-5 days and up to 1,000 mg methylprednisolone/day. After 6 months, Phase 2, the same Phase 1 regimen applied.

| Reporting group title | Waiting |
|---|---|

Reporting group description:

Fingolimod as baseline immunomodulatory multiple sclerosis treatment is prescribed as per clinical practice. During Phase 1, participants randomized to this arm did not receive e-training exercise. After a 6 month waiting period, phase 2, participants had an introductory group session, hosted by a sports therapist. The individual training schedule was comprised of strength exercises twice a week for 30-45 minutes and endurance training once a week for 20-60 minutes for 6 months. The participants documented each training session thoroughly via the web-based application (duration, type of exercises, number of repetitions and sets, perceived exertion). A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses as clinically warranted. Steroid treatment consisted of 3-5 days and up to 1,000 mg methylprednisolone/day.

| Reporting group title | E-training |
|---|---|

Reporting group description:

Fingolimod as baseline immunomodulatory multiple sclerosis treatment was prescribed as per clinical practice. During phase 1, participants randomized to this arm had an introductory group session, hosted by a sports therapist. The individual training schedule was comprised of strength exercises twice a week for 30-45 minutes and endurance training once a week for 20-60 minutes for 6 months. The participants documented each training session thoroughly via the web-based application (duration, type of exercises, number of repetitions and sets, perceived exertion). A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses as clinically warranted. Steroid treatment consisted of 3-5 days and up to 1,000 mg methylprednisolone/day. After 6 months, Phase 2, the same Phase 1 regimen applied.

| Reporting group title | Waiting |
|---|---|

Reporting group description:

Fingolimod as baseline immunomodulatory multiple sclerosis treatment is prescribed as per clinical practice. During Phase 1, participants randomized to this arm did not receive e-training exercise. After a 6 month waiting period, phase 2, participants had an introductory group session, hosted by a sports therapist. The individual training schedule was comprised of strength exercises twice a week for 30-45 minutes and endurance training once a week for 20-60 minutes for 6 months. The participants documented each training session thoroughly via the web-based application (duration, type of exercises, number of repetitions and sets, perceived exertion). A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses as clinically warranted. Steroid treatment consisted of 3-5 days and up to 1,000 mg methylprednisolone/day.

### Primary: Change from baseline in fatigue as measured by the Modified Fatigue Impact Scale (mFIS ).

| End point title | Change from baseline in fatigue as measured by the Modified Fatigue Impact Scale (mFIS ). |
|---|---|

End point description:

The mFIS provides an assessment of the effects of fatigue in terms of physical, cognitive, and psychosocial functioning. It is a 21-item, structured, self-report questionnaire that generally can be completed with little or no intervention from an interviewer. The mFIS score ranged from 0 (not tired) to 84 (tired). A negative change from baseline indicates improvement.

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| Baseline, 6 months | |

| **End point values** | E-training | Waiting | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 56 | 83 | | |
| Units: score on a scale | | | | |
| least squares mean (confidence interval 95%) | -3.57 (-6.81 to -0.34) | -2.1 (-4.69 to 0.49) | | |

**Statistical analyses**

| **Statistical analysis title** | Change from baseline in fatigue by mFIS |
|---|---|
| Comparison groups | E-training v Waiting |
| Number of subjects included in analysis | 139 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4579 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.39 |
| upper limit | 2.44 |

**Secondary: Change from baseline in isometric and dynamic muscular strength as measured by sit-to-stand test**

| End point title | Change from baseline in isometric and dynamic muscular strength as measured by sit-to-stand test |
|---|---|

End point description:

The Sit to Stand Test is a functional outcome measure of the lower-extremity muscle power. The test was performed 3 times with one minute rest in between. The best attempt out of three was used for the analysis. A positive change from baseline indicates improvement.

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| baseline, 6 months | |

| End point values | E-training | Waiting | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 83 | | |
| Units: watt/kilogram body weight | | | | |
| least squares mean (confidence interval 95%) | 0.03 (-0.31 to 0.36) | 0.27 (-0.01 to 0.55) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in isometric and dynamic muscular strength as measured by change in leg strength and trunk strength

| End point title | Change from baseline in isometric and dynamic muscular strength as measured by change in leg strength and trunk strength |
|---|---|

End point description:

Isometric and dynamic muscular strength was measured by an Isomed 2000 isometric measurement device (knee flexion/tension, trunk flexion/extension). Isomed 2000 device measures muscular flexion and tension under standardized training conditions. A positive change from baseline indicates improvement.

| End point type | Secondary |
|---|---|

End point timeframe:

baseline, 6 months

| End point values | E-training | Waiting | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 56 | 83 | | |
| Units: newton meter | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Leg strength | 0.5 (-1.83 to 2.83) | 1.63 (-0.32 to 3.58) | | |
| Trunk strength | 0.08 (-0.01 to 0.18) | 0.12 (0.04 to 0.2) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in isometric and dynamic muscular strength as measured by leg strength endurance

| End point title | Change from baseline in isometric and dynamic muscular strength as measured by leg strength endurance |
|---|---|

End point description:

Isometric and dynamic muscular strength was measured by an Isomed 2000 isometric measurement device (knee flexion/tension, trunk flexion/extension). Isomed 2000 device measures muscular flexion

and tension under standardized training conditions. A positive change from baseline indicates improvement.

| End point type | Secondary |
|---|---|

End point timeframe:

baseline, 6 months

| **End point values** | E-training | Waiting | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 56 | 83 | | |
| Units: joule | | | | |
| least squares mean (confidence interval 95%) | 51.28 (-50.7 to 153.3) | 130.8 (47.53 to 214.1) | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from baseline in quality of life as measured by the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS)**

| End point title | Change from baseline in quality of life as measured by the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS) |
|---|---|

End point description:

The Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS) consists of 44 items, 28 of which are the basis for computation of five subscale scores reflecting major dimensions of health-related quality of life (HRQoL) in MS: Fatigue/Thinking (4 items), Mobility lower limb (5 items), Mobility upper limb (5 items), Social function (6 items) and Mood (eight items). Subscales and total score range from 1 to 5, with high scores indicating a lower quality of life. In this study, the total score and following 3 subscales: fatigue/thinking, mobility lower limb and mobility upper limb only were analyzed. A negative change from baseline indicates improvement.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, 6 months, 12 months

| **End point values** | E-training | Waiting | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 56 | 83 | | |
| Units: score on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Total score | -0.11 (-0.21 to -0.01) | -0.02 (-0.1 to 0.06) | | |
| Fatigue/thinking | -0.3 (-0.48 to -0.12) | -0.16 (-0.3 to -0.01) | | |
| Mobility lower limb | 0 (-0.16 to 0.15) | 0.08 (-0.04 to 0.2) | | |

| | | | | |
|---|---|---|---|---|
| Mobility upper limb | 0 (-0.1 to 0.1) | 0.12 (0.04 to 0.2) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in fatigue as measured by the WEIMuS (Würzburg Fatigue Inventory for MS)

| End point title | Change from baseline in fatigue as measured by the WEIMuS (Würzburg Fatigue Inventory for MS) |
|---|---|

End point description:

The WEIMuS (Würzburg Fatigue Inventory for MS) scale is a validated self-assessment instrument to quantify the degree of fatigue. The scale consists of 17 items with 5 categories that are scored from '0' to '4'. The subscores for cognitive and physical fatigue range from 0 to 36 and from 0 to 32, respectively, with the total sum score ranging from 0 to 68; higher scores indicate higher degrees of fatigue. A negative change from baseline indicates improvement.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, 6 months

| End point values | E-training | Waiting | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 56 | 83 | | |
| Units: score on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.9 (-4.91 to 1.11) | -1.12 (-3.55 to 1.31) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in depression as measured by the Beck Depression Inventory Second Edition (BDI-II)

| End point title | Change from baseline in depression as measured by the Beck Depression Inventory Second Edition (BDI-II) |
|---|---|

End point description:

The Beck Depression Inventory Second Edition (BDI-II) is a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition. Each of the 21 items corresponding to a symptom of depression is summed to give a single score for the BDI-II. There is a four-point scale for each item ranging from 0 to 3. The total score ranges from 0 - 63. Total score of 0-13 is considered minimal range, 14-19 is mild, 20-28 is moderate, and 29-63 is severe. A negative change from baseline indicates improvement.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, 6 months

| End point values | E-training | Waiting | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 56 | 83 | | |
| Units: score on a scale | | | | |
| least squares mean (confidence interval 95%) | -2.62 (-4.42 to -0.81) | -1.97 (-3.43 to -0.52) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in aerobic capacity (VO2max) as measured by a physical endurance spiroergometry on a treadmill

| End point title | Change from baseline in aerobic capacity (VO2max) as measured by a physical endurance spiroergometry on a treadmill |
|---|---|

End point description:

Physical endurance spiroergometry was accomplished. Ergometry was assessed according to national guidelines of the German society for sports medicine. Ergometry is a combined examination of circulation and lung function and was performed as a submaximal or maximal test depending on the participant's individual performance. A negative change from baseline indicates improvement.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, 6 months

| End point values | E-training | Waiting | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 56 | 83 | | |
| Units: [ml/min/kg][watt/kg body weight] | | | | |
| least squares mean (confidence interval 95%) | -0.52 (-1.6 to 0.56) | -0.79 (-1.66 to 0.08) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in peak expiratory flow as measured by a physical endurance spiroergometry on a treadmill

| End point title | Change from baseline in peak expiratory flow as measured by a |
|---|---|

| | |
|---|---|
| | physical endurance spiroergometry on a treadmill |

End point description:

Physical endurance spiroergometry was accomplished. Ergometry was assessed according to national guidelines of the German society for sports medicine. Ergometry is a combined examination of circulation and lung function and was performed as a submaximal or maximal test depending on the participant's individual performance. A positive change from baseline indicates improvement.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline, 6 months

| **End point values** | E-training | Waiting | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 | 78 | | |
| Units: L/s | | | | |
| least squares mean (confidence interval 95%) | 0.05 (-0.15 to 0.24) | 0.01 (-0.15 to 0.17) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | e-training (1) |
| Reporting group description: e-training (1) | |
| Reporting group title | waiting (2) |
| Reporting group description: waiting (2) | |

| Serious adverse events | e-training (1) | waiting (2) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 9 / 84 (10.71%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| ASTROCYTOMA, LOW GRADE | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UTERINE LEIOMYOMA | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Injury, poisoning and procedural complications | | | |
| BONE CONTUSION | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONCUSSION | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DISLOCATION OF VERTEBRA | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RADIUS FRACTURE | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL FRACTURE | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| ARRHYTHMIA | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EXTRASYSTOLES | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PALPITATIONS | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Nervous system disorders | | | |
| EPILEPSY | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GENERALISED TONIC-CLONIC SEIZURE | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEMIPARESIS | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ISCHAEMIC CEREBRAL INFARCTION | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCLE SPASTICITY | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| MENORRHAGIA | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| INTERVERTEBRAL DISC PROTRUSION | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| APPENDICITIS PERFORATED | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | e-training (1) | waiting (2) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 58 / 94 (61.70%) | 59 / 84 (70.24%) | |
| Investigations | | | |
| BLOOD CHOLESTEROL INCREASED | | | |
| subjects affected / exposed | 2 / 94 (2.13%) | 5 / 84 (5.95%) | |
| occurrences (all) | 2 | 5 | |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 4 / 94 (4.26%) | 9 / 84 (10.71%) | |
| occurrences (all) | 4 | 10 | |
| Nervous system disorders | | | |
| HEADACHE | | | |
| subjects affected / exposed | 4 / 94 (4.26%) | 6 / 84 (7.14%) | |
| occurrences (all) | 5 | 7 | |
| MULTIPLE SCLEROSIS RELAPSE | | | |
| subjects affected / exposed | 22 / 94 (23.40%) | 15 / 84 (17.86%) | |
| occurrences (all) | 36 | 20 | |
| Gastrointestinal disorders | | | |
| DIARRHOEA | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 2 / 84 (2.38%) | |
| occurrences (all) | 5 | 2 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 3 / 94 (3.19%) | 8 / 84 (9.52%) | |
| occurrences (all) | 3 | 8 | |

| | | | |
|---|---|---|---|
| Psychiatric disorders | | | |
| DEPRESSION | | | |
| subjects affected / exposed | 4 / 94 (4.26%) | 8 / 84 (9.52%) | |
| occurrences (all) | 4 | 8 | |
| SLEEP DISORDER | | | |
| subjects affected / exposed | 10 / 94 (10.64%) | 4 / 84 (4.76%) | |
| occurrences (all) | 15 | 5 | |
| Musculoskeletal and connective tissue disorders | | | |
| BACK PAIN | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 5 / 84 (5.95%) | |
| occurrences (all) | 6 | 5 | |
| Infections and infestations | | | |
| BRONCHITIS | | | |
| subjects affected / exposed | 3 / 94 (3.19%) | 8 / 84 (9.52%) | |
| occurrences (all) | 4 | 10 | |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 34 / 94 (36.17%) | 33 / 84 (39.29%) | |
| occurrences (all) | 52 | 59 | |
| ORAL HERPES | | | |
| subjects affected / exposed | 6 / 94 (6.38%) | 2 / 84 (2.38%) | |
| occurrences (all) | 7 | 2 | |
| SINUSITIS | | | |
| subjects affected / exposed | 5 / 94 (5.32%) | 1 / 84 (1.19%) | |
| occurrences (all) | 6 | 1 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 5 / 84 (5.95%) | |
| occurrences (all) | 0 | 6 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 07 December 2011 | Amendment 1, resulted in protocol version 01 (including amendment 1) and was issued to implement corrections to the schedule of assessments and to make minor administrative corrections throughout the protocol. It could not be assured that the investigators were kept blinded within the study during patient interactions and therefore only the sports therapists should remain blinded. Randomization was to be performed by the investigator at the study site. The introductory weekend for the training group was integrated in the assessment schedule as Visit V2a. Furthermore, the safety reporting section was updated in terms of protocol exemptions: the randomization process was updated, updates were made to the assessment schedule table, the blood collection log was corrected to be conform with the assessment schedule and criteria for notable laboratory abnormalities were corrected. |
| 05 April 2012 | Amendment 2 resulted in protocol version 02 (including amendment 2) and was issued, when a "Dear Health Care Professional Letter" late January 2012 was issued to inform investigators about additional ECG-requirements for treatment initiation with fingolimod. In addition the protocol was amended to address recommendations of the committee for medicinal product for human use (CHMP) to strengthen cardiovascular monitoring during treatment initiation of fingolimod. The following changes were introduced (On 27 January 2012 the "Dear Health Care Professional Letter" was sent to all FTY720 study sites and the sites were informed that these recommendations were effective immediately.): • In this study, patients were treated with prescribed fingolimod as per clinical routine according to the current SmPC. Investigators were advised to comply with these recommendations for cardiovascular monitoring, as described in the "Dear Health Care Professional Letter", during treatment initiation and re-start of fingolimod after a treatment interruption for more than 14 days. In order to address a request of Ethics Committee, several cardiac exclusion criteria were further specified. |
| 19 June 2012 | Amendment 3 resulted in protocol version 03 (including amendment 3) and was issued to address final recommendations of the committee for medicinal product for human use CHMP and European Medicines Agency (EMA) with regards to cardiac response monitoring following the first dose of fingolimod. The EMA completed their review of fingolimod safety data on April 20, 2012. The recent recommendations of CHMP and EMA for the use of fingolimod were included in this amended protocol version: exclusion criterion no. 3 was specified according tothe CHMP recommendations for the use of fingolimod in patients with cardiac risks; in this study, patients were treated with prescribed fingolimod as per clinical routine according to the current SmPC. Investigators were advised to comply with these recommendations for cardiovascular monitoring, as described in the "Dear Health Care Professional Letter", during treatment initiation and re-start of fingolimod after a treatment interruption for more than 14 days. |

| | |
|---|---|
| 03 July 2013 | Amendment 4 resulted in protocol version 04 (including amendment 04) and was issued to implement an update to the fingolimod label in the EU approved by the CHMP. The updates to the label provided refined guidance on when existing first dose monitoring procedures should be repeated. The updates were submitted to the CHMP as a Type II Variation by Novartis. These recommendations were already included in the US Prescribing Information (PI) and were not related to any new safety reports. Both, the EMA and FDA, confirmed the positive benefit-risk profile of fingolimod when used in accordance with updated labels, which were announced earlier that year. Novartis informed healthcare professionals in the European Union of these recommendations via a Direct Healthcare Professional Communication (DHPC) by 11-Jan-2013. The following changes were introduced: in patients who were re- initiated after a certain treatment interruption a repetition of first-dose-monitoring strategy was necessary; in patients who required pharmacological intervention during the first dose monitoring and were monitored overnight in a medical facility the first dose monitoring should have been repeated after the second dose of fingolimod; and the AE reporting procedure has been corrected according to the process described in the assessment schedule. These amendments were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unblinding. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported