



Clinical trial results:

A 6-month, Randomized, Active Comparator, Open-label, Multi-Center Study to Evaluate Patient Outcomes, Safety and Tolerability of Fingolimod (FTY720) 0.5 mg/day in Patients with Relapsing Remitting Multiple Sclerosis who are candidates for MS therapy change from Previous Disease Modifying Therapy.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-024017-31 |
| Trial protocol | IT |
| Global end of trial date | 04 June 2014 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 13 July 2016 |
| First version publication date | 02 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CFTY720DIT02 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01317004 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Study Director, Novartis Pharma, AG, 41 613241111, |
| Scientific contact | Study Director, Novartis Pharma, AG, 41 613241111, |

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 | 04 June 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 June 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 June 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the change in patient-reported treatment satisfaction after six months of treatment with fingolimod 0.5mg/day vs. DMT standard of care using the global satisfaction subscale of the Treatment Satisfaction Questionnaire for Medication (TSQM-9).

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 | 25 May 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: 65 |
| Worldwide total number of subjects | 65 |
| EEA total number of subjects | 65 |

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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Actual enrollment = 61 because 65 participants were randomized to the study, but only 61 participants received at least one dose of study medication.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Multiple Sclerosis Disease Modifying Treatment (MS DMT) |

Arm description:

Patients randomized in this arm received selected Standard MS DMT such as Interferon beta-1b or Interferon beta-1a or Glatiramer acetate for 6 months.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | MS DMT |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Intravesical solution/solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Selected Standard MS Disease Modifying Treatment (DMT) such as Interferon beta-1b or Interferon beta-1a or Glatiramer acetate for 6 months.

| | |
|------------------|------------|
| Arm title | Fingolimod |
|------------------|------------|

Arm description:

Patients randomized in this arm received Fingolimod 0.5 mg/day oral capsule for 6 months core period.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Fingolimod |
| Investigational medicinal product code | FTY720 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Fingolimod 0.5 mg/day oral capsule for 6 months.

| Number of subjects in period 1 ^[1] | Multiple Sclerosis Disease Modifying Treatment (MS DMT) | Fingolimod |
|--|--|------------|
| | | |
| Started | 11 | 50 |
| Completed | 5 | 47 |
| Not completed | 6 | 3 |
| Consent withdrawn by subject | 1 | - |
| Adverse event, non-fatal | 3 | 3 |
| Protocol deviation | 2 | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Actual enrollment = 61 because 65 participants were randomized to the study, but only 61 participants received at least one dose of study medication.

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Fingolimod |
| Reporting group description: | |
| Patients randomized in this arm received Fingolimod 0.5 mg/day oral capsule for 6 months core period. | |
| Reporting group title | Multiple Sclerosis Disease Modifying Treatment (MS DMT) |
| Reporting group description: | |
| Patients randomized in this arm received selected Standard MS DMT such as Interferon beta-1b or Interferon beta-1a or Glatiramer acetate for 6 months. | |

| Reporting group values | Fingolimod | Multiple Sclerosis Disease Modifying Treatment (MS DMT) | Total |
|--|------------|---|-------|
| Number of subjects | 50 | 11 | 61 |
| 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) | 50 | 11 | 61 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 37.96 | 35.82 | |
| standard deviation | ± 8.69 | ± 7.22 | - |
| Gender, Male/Female | | | |
| Units: Participants | | | |
| Female | 32 | 8 | 40 |
| Male | 18 | 3 | 21 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Multiple Sclerosis Disease Modifying Treatment (MS DMT) |
| Reporting group description: Patients randomized in this arm received selected Standard MS DMT such as Interferon beta-1b or Interferon beta-1a or Glatiramer acetate for 6 months. | |
| Reporting group title | Fingolimod |
| Reporting group description: Patients randomized in this arm received Fingolimod 0.5 mg/day oral capsule for 6 months core period. | |

Primary: Change from baseline in patient-reported treatment satisfaction

| | |
|---|---|
| End point title | Change from baseline in patient-reported treatment satisfaction |
| End point description: The Treatment Satisfaction Questionnaire for Medication (TSQM-9) is a psychometric measure of a patient's satisfaction with medication. It consists of 3 subscales: effectiveness, convenience and global satisfaction. The scores were computed by adding items for each domain, i.e. 1 to 3 for effectiveness, 4 - 6 for convenience and 7 to 9 for global satisfaction. The lowest possible score (1 for each item and 3 for all 3 subscales) was subtracted from the composite score and divided by the greatest possible score range. The greatest range was (7-1) X 3 items = 18 for the effectiveness and convenience, and (5-1) x 3 items = 12 for global satisfaction. This provided a transformed score between 0 and 1 that was then multiplied by 100. A positive change from baseline indicates improvement. | |
| End point type | Primary |
| End point timeframe: baseline, 6 months | |

| End point values | Fingolimod | Multiple Sclerosis Disease Modifying Treatment (MS DMT) | | |
|--------------------------------------|-----------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 | 10 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 19.57 (± 21) | 5.83 (± 16.47) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Change from Baseline |
| Comparison groups | Fingolimod v Multiple Sclerosis Disease Modifying Treatment (MS DMT) |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Change from baseline in patient-reported Activities of Daily Living (ADL)

| | |
|-----------------|---|
| End point title | Change from baseline in patient-reported Activities of Daily Living (ADL) |
|-----------------|---|

End point description:

The PRIMUS activity measure is a 15-item assessment used to evaluate patient-reported activities of daily living. The PRIMUS activities score was calculated summing the 15 items, after recoding the responses from 1 - 3 to 0 - 2. Therefore, the total score ranged from 0 - 3-, where high scores were indicative of greater function limitation. A negative change from baseline indicates improvement.

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

End point timeframe:

baseline, 6 months

| End point values | Fingolimod | Multiple Sclerosis Disease Modifying Treatment (MS DMT) | | |
|--------------------------------------|-----------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 49 | 11 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.19 (± 2.75) | 0.15 (± 1.72) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in patient-reported fatigue

| | |
|-----------------|--|
| End point title | Change from baseline in patient-reported fatigue |
|-----------------|--|

End point description:

The fatigue Severity Scale (FSS) is a 9-item scale used to assess fatigue. The FSS score was calculated summing the 9 items of the questionnaire and dividing by the number of non-missing items (each item is based on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree)). A negative change from baseline indicates improvement.

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

End point timeframe:

6 months

| End point values | Fingolimod | Multiple Sclerosis Disease Modifying Treatment (MS DMT) | | |
|--------------------------------------|-----------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 11 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | -0.18 (± 1.46) | -0.32 (± 1.21) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in patient-reported effectiveness and convenience

| | |
|-----------------|--|
| End point title | Change from baseline in patient-reported effectiveness and convenience |
|-----------------|--|

End point description:

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) is a psychometric measure of a patient's satisfaction with medication. It consists of 3 subscales: effectiveness, convenience and global satisfaction. The scores were computed by adding items for each domain, i.e. 1 to 3 for effectiveness, 4 - 6 for convenience and 7 to 9 for global satisfaction. The lowest possible score (1 for each item and 3 for all 3 subscales) was subtracted from the composite score and divided by the greatest possible score range. The greatest range was (7-1) X 3 items = 18 for the effectiveness and convenience, and (5-1) x 3 items = 12 for global satisfaction. This provided a transformed score between 0 and 1 that was then multiplied by 100. A positive change from baseline indicates improvement.

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

End point timeframe:

6 months

| End point values | Fingolimod | Multiple Sclerosis Disease Modifying Treatment (MS DMT) | | |
|--------------------------------------|-----------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 | 10 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Effectiveness | 13.53 (± 28.39) | -1.67 (± 32.4) | | |
| Convenience | 24.64 (± 18.28) | 12.78 (± 25.26) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in patient-reported depression

| | |
|-----------------|---|
| End point title | Change from baseline in patient-reported depression |
|-----------------|---|

End point description:

The Beck Depression Inventory Fast Screen (BDI-FS) is a brief, multiple choice, self reported inventory designed to evaluate depression in patients with medical illness. The BDI-FS score was calculated summing the 7 items of the questionnaire. Each item ranged from 0 (not present) to 3 (severe). The total score ranges from 0-3 (minimal depression), 4-8 (mild depression), 9-12 (moderate depression) and 13-21 (severe depression). A negative change from baseline indicates improvement.

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

End point timeframe:

6 months

| End point values | Fingolimod | Multiple Sclerosis Disease Modifying Treatment (MS DMT) | | |
|--------------------------------------|-----------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 11 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | -1.15 (± 3.59) | -0.12 (± 3.06) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in patient-reported health related quality of life (QOL)

| | |
|-----------------|---|
| End point title | Change from baseline in patient-reported health related quality of life (QOL) |
|-----------------|---|

End point description:

The SF-36v2 is a validated health-related quality of life instrument used in numerous disease states, including MS. It is a self-administered survey that measures 8 domains of health including: physical functioning, role limitations due to physical health, pain, general health, energy/fatigue, social functioning, role limitations due to emotional problems and emotional well-being. Additionally, two summary scale scores can be calculated: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). If half or more questions within a domain were answered, then a score was calculated for that domain. Otherwise, the patient score for that domain was set to missing. If the patient was missing any 1 of the 8 scale scores, then the physical and mental component scores were set to missing. An algorithm was used to create a score from 0 to 100 for each domain score and component score. A positive change from baseline indicates improvement.

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

End point timeframe:

6 months

| End point values | Fingolimod | Multiple Sclerosis Disease Modifying Treatment (MS DMT) | | |
|--|-----------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 9 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical functioning (n=41,9) | 1.71 (± 23.07) | -1.11 (± 20.73) | | |
| Role limitations due to physical health (n=42,9) | 7.14 (± 37.97) | 5.56 (± 27.32) | | |
| Pain (n=45,9) | 6.56 (± 24.32) | 14.44 (± 15.25) | | |
| General health (n=44,8) | 4.52 (± 19.43) | 6.25 (± 14.08) | | |
| Energy/fatigue (n=43,9) | 2.33 (± 18.81) | 6.48 (± 33.24) | | |
| Social functioning (n=45,9) | 7.78 (± 24.9) | 6.94 (± 25.85) | | |
| Role limitations d/t emotional problems (n=45,9) | 7.04 (± 41.82) | 3.7 (± 38.89) | | |
| Emotional well-being (n=43,9) | 2.51 (± 16.88) | 4.89 (± 28.13) | | |
| PCS (n=40,8) | 4.52 (± 18.05) | 7.83 (± 15.86) | | |
| MCS (n=40,8) | 5.88 (± 18.21) | 7.28 (± 24.05) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Physician-reported Clinical Global Impression of Improvement (CGI-I)

| | |
|-----------------|--|
| End point title | Physician-reported Clinical Global Impression of Improvement (CGI-I) |
|-----------------|--|

End point description:

The CGI-I is a rating scale allowing a physician-reported global evaluation of the subject's improvement over time. The Investigator assessed the subject's clinical change relative to the symptoms at baseline on the CGI-I, a seven-point scale, with rating as follows: 1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No change, 5=Minimally worse, 6=Much worse, 7=Very much worse. A lower score and a negative change from baseline indicate improvement.

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

End point timeframe:

6 months

| End point values | Fingolimod | Multiple Sclerosis Disease Modifying Treatment (MS DMT) | | |
|-----------------------------------|-----------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 9 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |

| | | | | |
|--------------------|-------|-------|--|--|
| Much improved | 13.64 | 11.11 | | |
| Minimally improved | 36.36 | 11.11 | | |
| No change | 47.73 | 66.67 | | |
| Minimally worse | 2.27 | 11.11 | | |

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

Adverse event reporting additional description:

AE additional description

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 13.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Fingolimod |
|-----------------------|------------|

Reporting group description:

Fingolimod

| | |
|-----------------------|-----------------|
| Reporting group title | Standard MS DMT |
|-----------------------|-----------------|

Reporting group description:

Standard MS DMT

| Serious adverse events | Fingolimod | Standard MS DMT | |
|---|----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 1 / 11 (9.09%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Human papilloma virus test positive | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 11 (9.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Meningioma | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Multiple sclerosis relapse | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Lymphopenia | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 11 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Drug ineffective | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Fingolimod | Standard MS DMT | |
|---|------------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 29 / 50 (58.00%) | 7 / 11 (63.64%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cyst | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 1 | 1 | |
| Injection site reaction | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reproductive system and breast disorders | | | |
| Testicular disorder | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Upper respiratory tract inflammation | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gamma-glutamyltransferase increased | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Contusion | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac disorders | | | |
| Brugada syndrome | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lymphopenia | | | |
| subjects affected / exposed | 8 / 50 (16.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 8 | 0 | |

| | | |
|--|--------------------------------|--|
| <p>Eye disorders</p> <p>Conjunctival haemorrhage</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 50 (2.00%)</p> <p>1</p> | <p>0 / 11 (0.00%)</p> <p>0</p> | |
| <p>Vision blurred</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>0 / 50 (0.00%)</p> <p>0</p> | <p>1 / 11 (9.09%)</p> <p>1</p> | |
| <p>Gastrointestinal disorders</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>0 / 50 (0.00%)</p> <p>0</p> | <p>1 / 11 (9.09%)</p> <p>1</p> | |
| <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 50 (2.00%)</p> <p>1</p> | <p>0 / 11 (0.00%)</p> <p>0</p> | |
| <p>Dyspepsia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 50 (2.00%)</p> <p>1</p> | <p>0 / 11 (0.00%)</p> <p>0</p> | |
| <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>0 / 50 (0.00%)</p> <p>0</p> | <p>1 / 11 (9.09%)</p> <p>1</p> | |
| <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>0 / 50 (0.00%)</p> <p>0</p> | <p>1 / 11 (9.09%)</p> <p>1</p> | |
| <p>Hepatobiliary disorders</p> <p>Hypertransaminasaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 50 (2.00%)</p> <p>1</p> | <p>1 / 11 (9.09%)</p> <p>1</p> | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Alopecia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 50 (2.00%)</p> <p>1</p> | <p>0 / 11 (0.00%)</p> <p>0</p> | |
| <p>Eczema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 50 (2.00%)</p> <p>1</p> | <p>0 / 11 (0.00%)</p> <p>0</p> | |
| <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>0 / 50 (0.00%)</p> <p>0</p> | <p>1 / 11 (9.09%)</p> <p>1</p> | |

| | | | |
|---|---------------------|---------------------|--|
| Rash erythematous subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 11 (0.00%) 0 | |
| Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 11 (0.00%) 0 | |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Musculoskeletal and connective tissue disorders Muscle contracture subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 11 (0.00%) 0 | |
| Infections and infestations Influenza subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 0 / 11 (0.00%) 0 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 11 (0.00%) 0 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 2 | 0 / 11 (0.00%) 0 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 11 (0.00%) 0 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Dyslipidaemia subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 11 (0.00%) 0 | |
| Hypercholesterolaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 27 February 2013 | Amendment 1: The main purpose of amendment 1 was to allow patients completing this study to be included in CFTY720DIT07, an open-label study aimed at guaranteeing therapeutic continuity to patients who had completed international or local studies of fingolimod (CFTY720D2399, CFTY720DIT01, CFTY720DIT02, CFTY720DIT03) but were not eligible for drug reimbursement from the Italian National Health Service and did not have any other valid therapeutic option. Furthermore, the study aimed to generate long-term safety and tolerability data in a population that was different from the one treated in normal clinical practice, according to the indications currently approved in Italy. Protocol CFTY720DIT07 initially called for the enrollment of roughly 200 patients. However, the number of patients that needed to continue therapy was actually only 25, a number not compatible with some of the above-mentioned objectives due to the reduced significance of the tolerability and safety data emerging from such a limited number of cases. This amendment also clarified Exclusion criterion related to patients with an acute relapse of MS added. Better clarification of exclusion of patients with chronic diseases of the immune system. Exclusion criteria related to cardiovascular conditions updated. Exclusion of patients taking medications that lower heart rate added. Exclusion criterion concerning prior intake of fingolimod added. Exclusion criterion related to prior participation in a clinical trial with other S1P-receptor modulators added. Appendix 4 "Guidance for observation of patients taking their first dose of fingolimod" updated to reflect final CHMP recommendations. Safety monitoring guidelines updated to reflect fingolimod prescribing information. |
| 16 December 2013 | Amendment 2: It was decided that the need to guarantee therapeutic continuity in situations as these could be met more simply and adequately through a compassionate use program, as per Ministerial Decree May 8, 2003. Therefore, Novartis continued to provide the drug on an individual basis to guarantee therapeutic continuity to patients in treatment with Gilenya who were present for their end of study visit. Amendment 2 also clarified the Protocol Synopsis section: ,Study completion and post-study treatment: information on study CFTY720DIT07 deleted. Background: information updated with cumulative data from clinical studies (cutoff date 31 August 2013). Clarification on MS Relapse Activity and Reporting: corticosteroid usage for treatment of relapse and Exclusion Criteria: inconsistency regarding the timeframe before re-screening after virus zoster vaccination corrected. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported