



## Clinical trial results:

**A 3-year multi-center study to describe the long term changes of optical coherence tomography (OCT) parameters in patients under treatment with Gilenya®**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-000674-31   |
| Trial protocol           | DE               |
| Global end of trial date | 18 February 2019 |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 01 March 2020 |
| First version publication date | 01 March 2020 |

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | CFTY720DDE15TS |
|-----------------------|----------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01705236 |
| 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, Novartis.email@novartis.com |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |

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                       | 18 February 2019 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 18 February 2019 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the change in average RNFL thickness (RNFLT) in RRMS subjects treated with fingolimod over 36 months as assessed by OCT.

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                          | 20 August 2012 |
| 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: 77     |
| Country: Number of subjects enrolled | Switzerland: 10 |
| Worldwide total number of subjects   | 87              |
| EEA total number of subjects         | 77              |

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)                      | 87 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were screened at 10 study centers in Germany (9 centers) and Switzerland (1 center).

### Pre-assignment

Screening details:

Subjects who passed the screening were enrolled in the trial.

### Period 1

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

### Arms

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Fingolimod - Longitudinal Assessment |
|------------------|--------------------------------------|

Arm description:

No study drug was provided. Fingolimod was to be prescribed according to local label. The decision to prescribe fingolimod was to be made independent of this study.

|                                        |              |
|----------------------------------------|--------------|
| 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 was to be prescribed according to local label. The decision to prescribe fingolimod was to be made independent of this study.

| Number of subjects in period 1    | Fingolimod - Longitudinal Assessment |
|-----------------------------------|--------------------------------------|
| Started                           | 87                                   |
| Completed                         | 60                                   |
| Not completed                     | 27                                   |
| Abnormal laboratory value(s)      | 4                                    |
| Consent withdrawn by subject      | 5                                    |
| Adverse event, non-fatal          | 5                                    |
| Unsatisfactory therapeutic effect | 3                                    |
| Administrative problems           | 2                                    |
| Lost to follow-up                 | 1                                    |
| Abnormal test procedure result(s) | 4                                    |
| Protocol deviation                | 3                                    |



## Baseline characteristics

### Reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Fingolimod - Longitudinal Assessment |
|-----------------------|--------------------------------------|

Reporting group description:

No study drug was provided. Fingolimod was to be prescribed according to local label. The decision to prescribe fingolimod was to be made independent of this study.

| Reporting group values                             | Fingolimod - Longitudinal Assessment | Total |  |
|----------------------------------------------------|--------------------------------------|-------|--|
| Number of subjects                                 | 87                                   | 87    |  |
| Age categorical<br>Units: Subjects                 |                                      |       |  |
| In utero                                           | 0                                    | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0                                    | 0     |  |
| Newborns (0-27 days)                               | 0                                    | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0                                    | 0     |  |
| Children (2-11 years)                              | 0                                    | 0     |  |
| Adolescents (12-17 years)                          | 0                                    | 0     |  |
| Adults (18-64 years)                               | 87                                   | 87    |  |
| From 65-84 years                                   | 0                                    | 0     |  |
| 85 years and over                                  | 0                                    | 0     |  |
| Age Continuous<br>Units: Years                     |                                      |       |  |
| arithmetic mean                                    | 35.9                                 |       |  |
| standard deviation                                 | ± 9.5                                | -     |  |
| Sex: Female, Male<br>Units: Participants           |                                      |       |  |
| Female                                             | 55                                   | 55    |  |
| Male                                               | 32                                   | 32    |  |
| Race/Ethnicity, Customized<br>Units: Subjects      |                                      |       |  |
| Caucasian                                          | 84                                   | 84    |  |
| Other                                              | 3                                    | 3     |  |

## End points

### End points reporting groups

|                                                                                                                                                                      |                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Reporting group title                                                                                                                                                | Fingolimod - Longitudinal Assessment |
| Reporting group description:                                                                                                                                         |                                      |
| No study drug was provided. Fingolimod was to be prescribed according to local label. The decision to prescribe fingolimod was to be made independent of this study. |                                      |

### Primary: Change from baseline to month 36 in average Retinal Nerve Fiber Layer Thickness (RNFLT)

|                                                                                                                                                                                                                                                                                                                                            |                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                            | Change from baseline to month 36 in average Retinal Nerve Fiber Layer Thickness (RNFLT) <sup>[1]</sup> |
| End point description:                                                                                                                                                                                                                                                                                                                     |                                                                                                        |
| The primary endpoint was the change, i.e. the absolute difference, in average RNFL thickness from baseline to month 36 (or last values in case of missing data) in the Full Analysis Set (FAS). Average RNFL thickness was the average of valid measurements of the right and left eye and assessed by optical coherence tomography (OCT). |                                                                                                        |
| End point type                                                                                                                                                                                                                                                                                                                             | Primary                                                                                                |
| End point timeframe:                                                                                                                                                                                                                                                                                                                       |                                                                                                        |
| Baseline, month 36                                                                                                                                                                                                                                                                                                                         |                                                                                                        |
| Notes:                                                                                                                                                                                                                                                                                                                                     |                                                                                                        |
| [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.                                                                                                                                                                        |                                                                                                        |
| Justification: single arm trial.                                                                                                                                                                                                                                                                                                           |                                                                                                        |

|                                      |                                      |  |  |  |
|--------------------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>              | Fingolimod - Longitudinal Assessment |  |  |  |
| Subject group type                   | Reporting group                      |  |  |  |
| Number of subjects analysed          | 72                                   |  |  |  |
| Units: micrometer                    |                                      |  |  |  |
| arithmetic mean (standard deviation) | -1.5 (± 2.7)                         |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to month 12 and 24 in average Retinal Nerve Fiber Layer Thickness (RNFLT)

|                                                                                                                                                                                                                                                                                        |                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                        | Change from baseline to month 12 and 24 in average Retinal Nerve Fiber Layer Thickness (RNFLT) |
| End point description:                                                                                                                                                                                                                                                                 |                                                                                                |
| Change from baseline in average RNFL thickness to months 12 and 24 (or last values in case of missing data) in the Full Analysis Set (FAS). Average RNFL thickness was the average of valid measurements of the right and left eye and assessed by optical coherence tomography (OCT). |                                                                                                |
| End point type                                                                                                                                                                                                                                                                         | Secondary                                                                                      |
| End point timeframe:                                                                                                                                                                                                                                                                   |                                                                                                |
| Baseline, month 12, month 24                                                                                                                                                                                                                                                           |                                                                                                |

| End point values                     | Fingolimod - Longitudinal Assessment |  |  |  |
|--------------------------------------|--------------------------------------|--|--|--|
| Subject group type                   | Reporting group                      |  |  |  |
| Number of subjects analysed          | 72                                   |  |  |  |
| Units: micrometer                    |                                      |  |  |  |
| arithmetic mean (standard deviation) |                                      |  |  |  |
| Change from baseline to month 12     | -0.8 (± 2.4)                         |  |  |  |
| Change from baseline to month 24     | -1.1 (± 2.4)                         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to month 12, 24 and 36 in average quadrant Retinal Nerve Fiber Layer Thickness (RNFLT)

|                 |                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline to month 12, 24 and 36 in average quadrant Retinal Nerve Fiber Layer Thickness (RNFLT) |
|-----------------|-------------------------------------------------------------------------------------------------------------|

End point description:

Change from baseline in average quadrant RNFL thickness to months 12, 24 and 36 (or last values in case of missing data) in the Full Analysis Set (FAS). Average quadrant RNFL thickness was the average of valid measurements of the right and left eye and assessed by optical coherence tomography (OCT). Quadrant RNFL thickness were: Nasal-inferior; nasal-superior; temporal-inferior; temporal-superior.

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

End point timeframe:

Baseline, month 12, month 24, month 36

| End point values                           | Fingolimod - Longitudinal Assessment |  |  |  |
|--------------------------------------------|--------------------------------------|--|--|--|
| Subject group type                         | Reporting group                      |  |  |  |
| Number of subjects analysed                | 72                                   |  |  |  |
| Units: micrometer                          |                                      |  |  |  |
| arithmetic mean (standard deviation)       |                                      |  |  |  |
| Nasal-superior RNFL thickness: month 12    | 0.5 (± 4.0)                          |  |  |  |
| Nasal-superior RNFL thickness: month 24    | -0.4 (± 3.4)                         |  |  |  |
| Nasal-superior RNFL thickness: month 36    | -0.7 (± 3.9)                         |  |  |  |
| Nasal-inferior RNFL thickness: month 12    | -1.2 (± 4.9)                         |  |  |  |
| Nasal-inferior RNFL thickness: month 24    | -1.6 (± 5.1)                         |  |  |  |
| Nasal-inferior RNFL thickness: month 36    | -2.1 (± 5.2)                         |  |  |  |
| Temporal-inferior RNFL thickness: month 12 | -1.2 (± 2.5)                         |  |  |  |
| Temporal-inferior RNFL thickness: month 24 | -1.6 (± 3.1)                         |  |  |  |

|                                               |                   |  |  |  |
|-----------------------------------------------|-------------------|--|--|--|
| Temporal-inferior RNFL thickness:<br>month 36 | -2.3 ( $\pm$ 4.1) |  |  |  |
| Temporal-superior RNFL thickness:<br>month 12 | -0.5 ( $\pm$ 3.9) |  |  |  |
| Temporal-superior RNFL thickness:<br>month 24 | -0.4 ( $\pm$ 3.4) |  |  |  |
| Temporal-superior RNFL thickness:<br>month 36 | -1.1 ( $\pm$ 4.1) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline to month 12, 24 and 36 in Total Macular Volume (TMV)

|                                                                                                                                                        |                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| End point title                                                                                                                                        | Change from baseline to month 12, 24 and 36 in Total Macular Volume (TMV) |
| End point description:<br>Change from baseline in TMV to months 12, 24 and 36 (or last values in case of missing data) in the Full Analysis Set (FAS). |                                                                           |
| End point type                                                                                                                                         | Secondary                                                                 |
| End point timeframe:<br>12, 24 and 36 months                                                                                                           |                                                                           |

| End point values                     | Fingolimod - Longitudinal Assessment |  |  |  |
|--------------------------------------|--------------------------------------|--|--|--|
| Subject group type                   | Reporting group                      |  |  |  |
| Number of subjects analysed          | 72                                   |  |  |  |
| Units: Cubic millimeter              |                                      |  |  |  |
| arithmetic mean (standard deviation) |                                      |  |  |  |
| Change from baseline to month 12     | -0.03 ( $\pm$ 0.08)                  |  |  |  |
| Change from baseline to month 24     | -0.04 ( $\pm$ 0.08)                  |  |  |  |
| Change from baseline to month 36     | -0.06 ( $\pm$ 0.10)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline to month 12, 24 and 36 in Ganglion Cell Inner Plexiform (GCIP)

|                                                                                                                                                                                                                                                                                                                                                             |                                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                             | Change from baseline to month 12, 24 and 36 in Ganglion Cell Inner Plexiform (GCIP) |
| End point description:<br>Change from baseline in GCIP to months 12, 24 and 36 (or last values in case of missing data) in the Full Analysis Set (FAS).<br>The change in Ganglion cell layer thickness (GCLT) had been defined as secondary endpoint in the protocol, but OCT measured the GCIP instead. This was done because both layers were not clearly |                                                                                     |

separable by OCT. GCIP was calculated as mean of the inner sectors (nasal, superior, temporal, and inferior) and declared as usual parameter instead. This change was introduced prior to data base lock, but the derivation of GCIP was corrected after data base lock.

|                                        |           |
|----------------------------------------|-----------|
| End point type                         | Secondary |
| End point timeframe:                   |           |
| Baseline, month 12, month 24, month 36 |           |

|                                      |                                      |  |  |  |
|--------------------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>              | Fingolimod - Longitudinal Assessment |  |  |  |
| Subject group type                   | Reporting group                      |  |  |  |
| Number of subjects analysed          | 72                                   |  |  |  |
| Units: micrometer                    |                                      |  |  |  |
| arithmetic mean (standard deviation) |                                      |  |  |  |
| Change from baseline to month 12     | -0.49 (± 2.39)                       |  |  |  |
| Change from baseline to month 24     | -0.42 (± 2.74)                       |  |  |  |
| Change from baseline to month 36     | -0.46 (± 3.01)                       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with adverse events

|                                                                            |                                            |
|----------------------------------------------------------------------------|--------------------------------------------|
| End point title                                                            | Number of participants with adverse events |
| End point description:                                                     |                                            |
| Number of participants with adverse events and specifically macular edema. |                                            |
| End point type                                                             | Secondary                                  |
| End point timeframe:                                                       |                                            |
| 36 months                                                                  |                                            |

|                                    |                                      |  |  |  |
|------------------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>            | Fingolimod - Longitudinal Assessment |  |  |  |
| Subject group type                 | Reporting group                      |  |  |  |
| Number of subjects analysed        | 87                                   |  |  |  |
| Units: Participants                |                                      |  |  |  |
| No. of subjects with any AE        | 80                                   |  |  |  |
| No. of subjects with macular edema | 0                                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study Treatment until end of study treatment up to maximum duration of 36 months.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:

Total

| Serious adverse events                                              | Total            |  |  |
|---------------------------------------------------------------------|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed                                         | 11 / 87 (12.64%) |  |  |
| number of deaths (all causes)                                       | 0                |  |  |
| number of deaths resulting from adverse events                      | 0                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| CERVIX CARCINOMA STAGE 0                                            |                  |  |  |
| subjects affected / exposed                                         | 1 / 87 (1.15%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| NASAL NEOPLASM                                                      |                  |  |  |
| subjects affected / exposed                                         | 1 / 87 (1.15%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| UTERINE LEIOMYOMA                                                   |                  |  |  |
| subjects affected / exposed                                         | 1 / 87 (1.15%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Injury, poisoning and procedural complications                      |                  |  |  |
| LOWER LIMB FRACTURE                                                 |                  |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>RADIUS FRACTURE</b>                          |                |  |  |
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>SUTURE RELATED COMPLICATION</b>              |                |  |  |
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Cardiac disorders</b>                        |                |  |  |
| <b>AORTIC VALVE INCOMPETENCE</b>                |                |  |  |
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Nervous system disorders</b>                 |                |  |  |
| <b>MULTIPLE SCLEROSIS RELAPSE</b>               |                |  |  |
| subjects affected / exposed                     | 2 / 87 (2.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>NEURALGIC AMYOTROPHY</b>                     |                |  |  |
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>UHTHOFF'S PHENOMENON</b>                     |                |  |  |
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Reproductive system and breast disorders</b> |                |  |  |
| <b>CERVICAL DYSPLASIA</b>                       |                |  |  |
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Musculoskeletal and connective tissue disorders |                |  |  |
| INTERVERTEBRAL DISC PROTRUSION                  |                |  |  |
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| ERYSIPELAS                                      |                |  |  |
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| GASTROENTERITIS VIRAL                           |                |  |  |
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| OPHTHALMIC HERPES ZOSTER                        |                |  |  |
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| WOUND INFECTION                                 |                |  |  |
| subjects affected / exposed                     | 1 / 87 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

|                                                       |                  |  |  |
|-------------------------------------------------------|------------------|--|--|
| <b>Non-serious adverse events</b>                     | Total            |  |  |
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 68 / 87 (78.16%) |  |  |
| Vascular disorders                                    |                  |  |  |
| HYPERTENSION                                          |                  |  |  |
| subjects affected / exposed                           | 12 / 87 (13.79%) |  |  |
| occurrences (all)                                     | 12               |  |  |
| Nervous system disorders                              |                  |  |  |

|                                                                                                                                 |                        |  |  |
|---------------------------------------------------------------------------------------------------------------------------------|------------------------|--|--|
| <b>DIZZINESS</b><br>subjects affected / exposed<br>occurrences (all)                                                            | 5 / 87 (5.75%)<br>5    |  |  |
| <b>HEADACHE</b><br>subjects affected / exposed<br>occurrences (all)                                                             | 10 / 87 (11.49%)<br>10 |  |  |
| <b>MULTIPLE SCLEROSIS RELAPSE</b><br>subjects affected / exposed<br>occurrences (all)                                           | 21 / 87 (24.14%)<br>31 |  |  |
| <b>PARAESTHESIA</b><br>subjects affected / exposed<br>occurrences (all)                                                         | 5 / 87 (5.75%)<br>5    |  |  |
| <b>Blood and lymphatic system disorders</b><br><b>LYMPHOPENIA</b><br>subjects affected / exposed<br>occurrences (all)           | 9 / 87 (10.34%)<br>10  |  |  |
| <b>Gastrointestinal disorders</b><br><b>DIARRHOEA</b><br>subjects affected / exposed<br>occurrences (all)                       | 6 / 87 (6.90%)<br>8    |  |  |
| <b>Respiratory, thoracic and mediastinal disorders</b><br><b>COUGH</b><br>subjects affected / exposed<br>occurrences (all)      | 6 / 87 (6.90%)<br>7    |  |  |
| <b>Skin and subcutaneous tissue disorders</b><br><b>ALOPECIA</b><br>subjects affected / exposed<br>occurrences (all)            | 5 / 87 (5.75%)<br>5    |  |  |
| <b>Psychiatric disorders</b><br><b>DEPRESSION</b><br>subjects affected / exposed<br>occurrences (all)                           | 5 / 87 (5.75%)<br>5    |  |  |
| <b>Musculoskeletal and connective tissue disorders</b><br><b>ARTHRALGIA</b><br>subjects affected / exposed<br>occurrences (all) | 5 / 87 (5.75%)<br>5    |  |  |
| <b>BACK PAIN</b>                                                                                                                |                        |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                 |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 7 / 87 (8.05%)<br>10                                                                                                                                            |  |  |
| Infections and infestations<br>BRONCHITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>CONJUNCTIVITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>NASOPHARYNGITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>SINUSITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>UPPER RESPIRATORY TRACT<br>INFECTION<br>subjects affected / exposed<br>occurrences (all)<br><br>URINARY TRACT INFECTION<br>subjects affected / exposed<br>occurrences (all) | 6 / 87 (6.90%)<br>8<br><br>5 / 87 (5.75%)<br>7<br><br>41 / 87 (47.13%)<br>68<br><br>6 / 87 (6.90%)<br>9<br><br>7 / 87 (8.05%)<br>13<br><br>7 / 87 (8.05%)<br>12 |  |  |
| Metabolism and nutrition disorders<br>VITAMIN D DEFICIENCY<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                             | 8 / 87 (9.20%)<br>8                                                                                                                                             |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 06 February 2013 | Implementation of an update of the Gilenya® (fingolimod) label providing refined guidance on when existing first dose monitoring procedures should be repeated after treatment interruption or after pharmacological intervention during first dose monitoring.                                                                                                                                                                                      |
| 27 March 2014    | Further definition of blood biomarker sampling was added and the period of one month was defined as 28 days. Furthermore, the specifications for contraception and for elevated liver function tests were adjusted and some inconsistencies within the protocol were corrected.                                                                                                                                                                      |
| 20 May 2015      | Blood biomarker sampling was removed from the protocol and a responsible person for OCT quality control was added.                                                                                                                                                                                                                                                                                                                                   |
| 26 July 2016     | Clarification that the minimum pre-treatment with fingolimod was 28 days and adaption of the visit schedule to the recommended visit schedule in the fingolimod product information which recommends visits every 3 months of treatment. Therefore, one month during the observational period of this study was re-defined as 28–31 days depending on the actual length of the respective month. The definition of one month as 28 days was removed. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported