



## Clinical trial results:

### A Multi-center, Randomized, Parallel-group, Rater-blinded Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis Plus a Long Term Extension Period

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2008-006226-34             |
| Trial protocol           | ES DE HU CZ IT GR FR BE GB |
| Global end of trial date | 13 May 2015                |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 25 May 2016  |
| First version publication date | 25 May 2016  |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | EFC10891 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                    |
|------------------------------------|--------------------|
| ISRCTN number                      | -                  |
| ClinicalTrials.gov id (NCT number) | NCT00883337        |
| WHO universal trial number (UTN)   | -                  |
| Other trial identifiers            | Study Name: TENERE |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Sanofi aventis recherche & développement   |
| Sponsor organisation address | 1 avenue Pierre Brossolette Chilly, Mazarin, France, 91380                               |
| Public contact               | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact           | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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                       | 20 July 2015 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 13 May 2015  |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

To assess the effectiveness of 2 doses of teriflunomide in comparison to interferon-beta 1 a, evaluated by the time to failure, with failure being defined as either relapse or permanent study treatment discontinuation for any cause whichever comes first.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial, the subject is participating in, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 16 April 2009 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 62         |
| Country: Number of subjects enrolled | Spain: 22          |
| Country: Number of subjects enrolled | United Kingdom: 5  |
| Country: Number of subjects enrolled | Belgium: 10        |
| Country: Number of subjects enrolled | Czech Republic: 21 |
| Country: Number of subjects enrolled | France: 41         |
| Country: Number of subjects enrolled | Germany: 55        |
| Country: Number of subjects enrolled | Greece: 3          |
| Country: Number of subjects enrolled | Hungary: 29        |
| Country: Number of subjects enrolled | Italy: 53          |
| Country: Number of subjects enrolled | Canada: 21         |
| Country: Number of subjects enrolled | Switzerland: 1     |
| Country: Number of subjects enrolled | Tunisia: 1         |
| Worldwide total number of subjects   | 324                |
| EEA total number of subjects         | 301                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 323 |
| From 65 to 84 years                       | 1   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The recruitment initiated in April 2009 was completed in July 2010. A total of 369 subjects were screened at 54 sites in 13 countries. The common end date of core treatment period was 14 September 2011 (maximum treatment duration of 115 weeks). The end date of extension was 13 May 2015 (maximum treatment duration of 197 weeks).

### Pre-assignment

Screening details:

Randomization was stratified by country and baseline disability (Expanded Disability Status Scale [EDSS] score  $\leq 3.5$  or  $>3.5$ ). Assignment to groups was done centrally using an Interactive Voice Response System (IVRS) in a 1:1:1 ratio after confirmation of the selection criteria. 324 subjects were randomized at 53 sites.

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Core Treatment Period   |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Single blind            |
| Roles blinded                | Assessor <sup>[1]</sup> |

### Arms

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | Teriflunomide 7 mg |

Arm description:

Teriflunomide 7 mg once daily for 48 weeks.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Teriflunomide      |
| Investigational medicinal product code | HMR1726            |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Teriflunomide orally as a single dose in the morning of each day with water and may be taken with or without food.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Teriflunomide 14 mg |
|------------------|---------------------|

Arm description:

Teriflunomide 14 mg once daily for 48 weeks.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Teriflunomide      |
| Investigational medicinal product code | HMR1726            |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Teriflunomide orally as a single dose in the morning of each day with water and may be taken with or without food. One Subject received teriflunomide 7 mg instead of teriflunomide 14 mg.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Interferon beta-1-a (IFN- $\beta$ -1a) |
|------------------|--|

Arm description:

IFN- $\beta$ -1a three times a week for 48 weeks.

|  |                        |
|--|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Interferon beta-1a     |
| Investigational medicinal product code |                        |
| Other name                             | Rebif®                 |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

IFN-β-1a subcutaneous (SC) injection at the same time on the same three days in the late afternoon or evening. Three subjects refused treatment with Rebif®.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: As per the trial design only assessor was blinded in the study.

| <b>Number of subjects in period 1</b> | Teriflunomide 7 mg | Teriflunomide 14 mg | Interferon beta-1-a (IFN-β-1a) |
|---------------------------------------|--------------------|---------------------|--------------------------------|
| Started                               | 109                | 111                 | 104                            |
| Treated                               | 109                | 111                 | 101                            |
| Completed                             | 89                 | 89                  | 71                             |
| Not completed                         | 20                 | 22                  | 33                             |
| Other than specified above            | -                  | 1                   | 1                              |
| Adverse event                         | 9                  | 12                  | 22                             |
| Poor compliance to protocol           | -                  | -                   | 1                              |
| Lost to follow-up                     | 1                  | 1                   | -                              |
| Wish to be pregnant                   | 1                  | 2                   | 1                              |
| Lack of efficacy                      | 7                  | 4                   | 2                              |
| Withdrawal by subject                 | 2                  | 2                   | 6                              |

## Period 2

|                              |                            |
|------------------------------|----------------------------|
| Period 2 title               | Extension Treatment Period |
| Is this the baseline period? | No                         |
| Allocation method            | Randomised - controlled    |
| Blinding used                | Single blind               |
| Roles blinded                | Assessor <sup>[2]</sup>    |

## Arms

|                              |                            |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes                        |
| <b>Arm title</b>             | Teriflunomide 7 mg / 14 mg |

Arm description:

Subjects received teriflunomide 7 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Teriflunomide      |
| Investigational medicinal product code | HMR1726            |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Teriflunomide orally as a single dose in the morning of each day with water and may be taken with or without food.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Teriflunomide 14 mg / 14 mg |
|------------------|-----------------------------|

Arm description:

Subjects received teriflunomide 14 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Teriflunomide      |
| Investigational medicinal product code | HMR1726            |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Teriflunomide orally as a single dose in the morning of each day with water and may be taken with or without food.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | IFN-β-1a / Teriflunomide 14 mg |
|------------------|--------------------------------|

Arm description:

Subjects received IFN-β-1a three times a week in core treatment period and teriflunomide 14 mg once daily in extension treatment period.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Teriflunomide      |
| Investigational medicinal product code | HMR1726            |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Teriflunomide orally as a single dose in the morning of each day with water and may be taken with or without food.

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: As per the trial design only assessor was blinded in the study.

| <b>Number of subjects in period 2<sup>[3]</sup></b> | Teriflunomide 7 mg / 14 mg | Teriflunomide 14 mg / 14 mg | IFN-β-1a / Teriflunomide 14 mg |
|---|----------------------------|-----------------------------|--------------------------------|
| Started   | 89                         | 89                          | 59                             |
| Completed   | 61                         | 66                          | 40                             |
| Not completed                                       | 28                         | 23                          | 19                             |
| Other than specified above                          | 10                         | 9                           | 5                              |
| Adverse event                                       | 8                          | 5                           | 5                              |
| Poor compliance to protocol                         | 1                          | 1                           | 1                              |
| Lost to follow-up                                   | 1                          | -                           | -                              |
| Lack of efficacy                                    | 8                          | 8                           | 8                              |

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Notes:

[3] - 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: 12 subjects completed the core period but didn't enter the extension period.

## Baseline characteristics

### Reporting groups

|  |                                |
|--|--------------------------------|
| Reporting group title  | Teriflunomide 7 mg             |
| Reporting group description:<br>Teriflunomide 7 mg once daily for 48 weeks.  |                                |
| Reporting group title  | Teriflunomide 14 mg            |
| Reporting group description:<br>Teriflunomide 14 mg once daily for 48 weeks. |                                |
| Reporting group title  | Interferon beta-1-a (IFN-β-1a) |
| Reporting group description:<br>IFN-β-1a three times a week for 48 weeks.    |                                |

| Reporting group values   | Teriflunomide 7 mg | Teriflunomide 14 mg | Interferon beta-1-a (IFN-β-1a) |
|--|--------------------|---------------------|--------------------------------|
| Number of subjects   | 109                | 111                 | 104                            |
| Age categorical<br>Units: Subjects   |                    |                     |                                |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation  | 32.5<br>± 9.2      | 36.8<br>± 10.3      | 37<br>± 10.6                   |
| Gender categorical<br>Units: Subjects  |                    |                     |                                |
| Female   | 70                 | 78                  | 71                             |
| Male   | 39                 | 33                  | 33                             |
| Region of Enrollment   |                    |                     |                                |
| Due the small sample size in some countries, the countries were pooled as follows:<br>- North America: Canada;<br>- Eastern Europe: Czech Republic, Greece, Hungary and Poland;<br>- Western Europe: Belgium, France, Germany, Italy, Spain, Switzerland and United Kingdom; subject in Tunisia was included in the Western Europe group.                                    |                    |                     |                                |
| Units: Subjects  |                    |                     |                                |
| North America  | 8                  | 6                   | 7                              |
| Eastern Europe   | 39                 | 41                  | 35                             |
| Western Europe   | 62                 | 64                  | 62                             |
| Multiple Sclerosis (MS) subtype<br>Units: Subjects   |                    |                     |                                |
| Relapsing Remitting  | 109                | 108                 | 104                            |
| Secondary Progressive  | 0                  | 1                   | 0                              |
| Progressive Relapsing  | 0                  | 2                   | 0                              |
| Baseline EDSS score  |                    |                     |                                |
| EDSS is an ordinal scale in half-point increments that qualifies disability in subjects with MS. It consists of 8 ordinal rating scales assessing seven functional systems (visual, brain-stem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS). |                    |                     |                                |
| Units: Subjects  |                    |                     |                                |
| ≤3.5   | 96                 | 95                  | 93                             |
| >3.5   | 13                 | 16                  | 11                             |



|  |                |                |                 |
|--|----------------|----------------|-----------------|
| Time since first diagnosis of MS<br>Units: years<br>arithmetic mean<br>standard deviation          | 3.72<br>± 5.19 | 3.68<br>± 6.24 | 3.82<br>± 5.69  |
| Time since most recent MS relapse onset  |                |                |                 |
| The information was not available for one subject in the Teriflunomide 14 mg group.                |                |                |                 |
| Units: months<br>arithmetic mean<br>standard deviation   | 9<br>± 13.96   | 7.9<br>± 10.34 | 9.79<br>± 10.72 |
| Number of MS relapses within the past year<br>Units: relapses<br>median<br>full range (min-max)    | 1<br>0 to 3    | 1<br>0 to 4    | 1<br>0 to 5     |
| Number of MS relapses within the past 2 years<br>Units: relapses<br>median<br>full range (min-max) | 2<br>0 to 4    | 2<br>0 to 4    | 2<br>0 to 6     |

|                                    |       |  |  |
|------------------------------------|-------|--|--|
| <b>Reporting group values</b>      | Total |  |  |
| Number of subjects                 | 324   |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

|  |     |  |  |
|--|-----|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation  | -   |  |  |
| Gender categorical<br>Units: Subjects  |     |  |  |
| Female   | 219 |  |  |
| Male   | 105 |  |  |
| Region of Enrollment   |     |  |  |
| Due the small sample size in some countries, the countries were pooled as follows:<br>- North America: Canada;<br>- Eastern Europe: Czech Republic, Greece, Hungary and Poland;<br>- Western Europe: Belgium, France, Germany, Italy, Spain, Switzerland and United Kingdom; subject in Tunisia was included in the Western Europe group.                                    |     |  |  |
| Units: Subjects  |     |  |  |
| North America  | 21  |  |  |
| Eastern Europe   | 115 |  |  |
| Western Europe   | 188 |  |  |
| Multiple Sclerosis (MS) subtype<br>Units: Subjects   |     |  |  |
| Relapsing Remitting  | 321 |  |  |
| Secondary Progressive  | 1   |  |  |
| Progressive Relapsing  | 2   |  |  |
| Baseline EDSS score  |     |  |  |
| EDSS is an ordinal scale in half-point increments that qualifies disability in subjects with MS. It consists of 8 ordinal rating scales assessing seven functional systems (visual, brain-stem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS). |     |  |  |

|  |     |  |  |
|--|-----|--|--|
| Units: Subjects  |     |  |  |
| ≤3.5   | 284 |  |  |
| >3.5   | 40  |  |  |
| Time since first diagnosis of MS<br>Units: years<br>arithmetic mean<br>standard deviation          | -   |  |  |
| Time since most recent MS relapse onset  |     |  |  |
| The information was not available for one subject in the Teriflunomide 14 mg group.                |     |  |  |
| Units: months<br>arithmetic mean<br>standard deviation   | -   |  |  |
| Number of MS relapses within the past year<br>Units: relapses<br>median<br>full range (min-max)    | -   |  |  |
| Number of MS relapses within the past 2 years<br>Units: relapses<br>median<br>full range (min-max) | -   |  |  |

## End points

### End points reporting groups

|   |                                |
|---|--------------------------------|
| Reporting group title   | Teriflunomide 7 mg             |
| Reporting group description:<br>Teriflunomide 7 mg once daily for 48 weeks.   |                                |
| Reporting group title   | Teriflunomide 14 mg            |
| Reporting group description:<br>Teriflunomide 14 mg once daily for 48 weeks.  |                                |
| Reporting group title   | Interferon beta-1-a (IFN-β-1a) |
| Reporting group description:<br>IFN-β-1a three times a week for 48 weeks.   |                                |
| Reporting group title   | Teriflunomide 7 mg / 14 mg     |
| Reporting group description:<br>Subjects received teriflunomide 7 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.      |                                |
| Reporting group title   | Teriflunomide 14 mg / 14 mg    |
| Reporting group description:<br>Subjects received teriflunomide 14 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.     |                                |
| Reporting group title   | IFN-β-1a / Teriflunomide 14 mg |
| Reporting group description:<br>Subjects received IFN-β-1a three times a week in core treatment period and teriflunomide 14 mg once daily in extension treatment period.        |                                |
| Subject analysis set title  | Teriflunomide 7 mg / 14 mg     |
| Subject analysis set type   | Safety analysis                |
| Subject analysis set description:<br>Subjects received teriflunomide 7 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period. |                                |
| Subject analysis set title  | Teriflunomide 7 mg / 14 mg     |
| Subject analysis set type   | Safety analysis                |
| Subject analysis set description:<br>Subjects received teriflunomide 7 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period. |                                |

### Primary: Core Treatment Period: Overview of Failures

|   |  |
|---|--|
| End point title   | Core Treatment Period: Overview of Failures <sup>[1]</sup> |
| End point description:<br>Failure was defined as the first occurrence of confirmed relapse or permanent treatment discontinuation (for any cause) which ever came first. If no events occurred, the subject was considered free of failure. Each episode of relapse appearance, or worsening of a clinical symptom that was stable for at least 30 days, that persisted for a minimum of 24 hours in the absence of fever was to be confirmed by an increase in EDSS score or Functional System scores. Intent-to-treat population: all randomized subjects. Subjects were considered in the treatment group to which they were randomized regardless of the drug they actually received. |  |
| End point type  | Primary  |
| End point timeframe:<br>Core treatment period between 48 and 118 weeks depending on when the subject was enrolled   |  |

#### 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: As data is descriptive in nature, no statistical analysis is performed.

| End point values            | Teriflunomide 7 mg | Teriflunomide 14 mg | Interferon beta-1-a (IFN- $\beta$ -1a) |  |
|-----------------------------|--------------------|---------------------|--|--|
| Subject group type          | Reporting group    | Reporting group     | Reporting group                        |  |
| Number of subjects analysed | 109                | 111                 | 104                                    |  |
| Units: Subjects             |                    |                     |  |  |
| Failure                     | 53                 | 42                  | 44                                     |  |
| Free of Failure             | 56                 | 69                  | 60                                     |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Core Treatment Period: Time to Failure: KaplanMeier Estimates of the Rate of Failure at Timepoints

|                 |  |
|-----------------|--|
| End point title | Core Treatment Period: Time to Failure: KaplanMeier Estimates of the Rate of Failure at Timepoints |
|-----------------|--|

End point description:

Probability of disability progression at 24, 48 and 96 weeks was estimated using Kaplan-Meier method on the time to failure defined as the time from randomization to failure. Subjects free of failure were censored at the date of last treatment. Kaplan-Meier method consists in computing probabilities of non-occurrence of event at any observed time of event and multiplying successive probabilities for time  $\leq t$  by any earlier computed probabilities to estimate the probability of being event-free for the amount of time t. Probability of event at time t is 1 minus the probability of being event-free for the amount of time t. ITT population.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Core treatment period between 48 and 118 weeks depending on when the subject was enrolled

| End point values                   | Teriflunomide 7 mg  | Teriflunomide 14 mg | Interferon beta-1-a (IFN- $\beta$ -1a) |  |
|------------------------------------|---------------------|---------------------|--|--|
| Subject group type                 | Reporting group     | Reporting group     | Reporting group                        |  |
| Number of subjects analysed        | 109                 | 111                 | 104                                    |  |
| Units: Percent probability         |                     |                     |  |  |
| number (confidence interval 95%)   |                     |                     |  |  |
| Probability of failure at 24 weeks | 25.7 (17.5 to 33.9) | 24.3 (16.3 to 32.3) | 29.8 (21 to 38.6)                      |  |
| Probability of failure at 48 weeks | 35.8 (26.8 to 44.8) | 33.3 (24.6 to 42.1) | 36.5 (27.3 to 45.8)                    |  |
| Probability of failure at 96 weeks | 58.8 (46.1 to 71.4) | 41.1 (30.9 to 51.4) | 44.4 (34.3 to 54.4)                    |  |

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Teriflunomide 14 mg vs IFN $\beta$ -1-a |
|----------------------------|---|

Statistical analysis description:

The study was sized to detect a difference between teriflunomide and Rebif groups in the time to failure at a significance level of 0.025 with a power of 81%.

Null hypothesis:

H1: No difference between teriflunomide 14 mg and Rebif

H2: No difference between teriflunomide 7 mg and Rebif

|   |  |
|---|--|
| Comparison groups                       | Teriflunomide 14 mg v Interferon beta-1-a (IFN-β-1a) |
| Number of subjects included in analysis | 215  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority <sup>[2]</sup>                           |
| P-value                                 | = 0.5953 <sup>[3]</sup>                              |
| Method                                  | Logrank  |

Notes:

[2] - Hochberg testing procedure:

-a-priori threshold for statistical significance  $\leq 0.05$  for the largest p-value of the 2 pair-wise comparisons.

-a-priori threshold for statistical significance  $\leq 0.025$  for the other p-value, if the largest p-value  $> 0.05$ .

[3] - Two-sided Log Rank test with the region of enrollment and baseline EDSS stratum as stratification factors.

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | Teriflunomide 7 mg vs IFNβ-1-a |
|-----------------------------------|--------------------------------|

Statistical analysis description:

Null hypothesis:

-H1: No difference between teriflunomide 14 mg and Rebif

-H2: No difference between teriflunomide 7 mg and Rebif

|   |   |
|---|---|
| Comparison groups                       | Teriflunomide 7 mg v Interferon beta-1-a (IFN-β-1a) |
| Number of subjects included in analysis | 213   |
| Analysis specification                  | Pre-specified                                       |
| Analysis type                           | superiority <sup>[4]</sup>                          |
| P-value                                 | = 0.519 <sup>[5]</sup>                              |
| Method                                  | Logrank   |

Notes:

[4] - Hochberg testing procedure:

-a-priori threshold for statistical significance  $\leq 0.05$  for the largest p-value of the 2 pair-wise comparisons.

-a-priori threshold for statistical significance  $\leq 0.025$  for the other p-value, if the largest p-value  $> 0.05$ .

[5] - Two-sided Log Rank test with the region of enrollment and baseline EDSS stratum as stratification factors.

## Secondary: Core Treatment Period: Annualized Relapse Rate [ARR] - Poisson Regression Estimates

|                 |   |
|-----------------|---|
| End point title | Core Treatment Period: Annualized Relapse Rate [ARR] - Poisson Regression Estimates |
|-----------------|---|

End point description:

ARR is obtained from the total number of confirmed relapses that occurred during the treatment period divided by the sum of the treatment durations. To account for the different treatment durations among subjects, a Poisson regression model with robust error variance was used (total number of confirmed relapses as response variable; log-transformed treatment duration as "offset" variable; treatment group, region of enrollment and baseline EDSS stratum as covariates). ITT population.

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

End point timeframe:

Core treatment period between 48 and 118 weeks depending on when the subject was enrolled.

| End point values                 | Teriflunomide 7 mg    | Teriflunomide 14 mg    | Interferon beta-1-a (IFN- $\beta$ -1a) |  |
|----------------------------------|-----------------------|------------------------|--|--|
| Subject group type               | Reporting group       | Reporting group        | Reporting group                        |  |
| Number of subjects analysed      | 109                   | 111                    | 104                                    |  |
| Units: Relapses per year         |                       |                        |  |  |
| number (confidence interval 95%) | 0.41 (0.265 to 0.636) | 0.259 (0.153 to 0.438) | 0.216 (0.113 to 0.415)                 |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Core Treatment Period: Change From Baseline in Fatigue Impact Scale (FIS) Total Score

|                 |   |
|-----------------|---|
| End point title | Core Treatment Period: Change From Baseline in Fatigue Impact Scale (FIS) Total Score |
|-----------------|---|

End point description:

FIS is a subject-reported scale that qualifies the impact of fatigue on daily life in subjects with MS. It consists of 40 statements that measure fatigue in three areas; physical, cognitive, and social. FIS total score ranges from 0 (no problem) to 160 (extreme problem). Least-square means were estimated using a Mixed-effect model with repeated measures [MMRM] on FIS total score data (treatment group, region of enrollment, baseline EDSS stratum, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as factors). ITT population.

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

End point timeframe:

Baseline (before randomization) and 48 weeks

| End point values                    | Teriflunomide 7 mg | Teriflunomide 14 mg | Interferon beta-1-a (IFN- $\beta$ -1a) |  |
|-------------------------------------|--------------------|---------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group     | Reporting group                        |  |
| Number of subjects analysed         | 109                | 111                 | 104                                    |  |
| Units: Units on a scale             |                    |                     |  |  |
| least squares mean (standard error) | 0.97 ( $\pm$ 2.96) | 4.1 ( $\pm$ 3.03)   | 9.1 ( $\pm$ 3.21)                      |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Core Treatment Period: Treatment Satisfaction Questionnaire for Medication [TSQM] Scores

|                 |  |
|-----------------|--|
| End point title | Core Treatment Period: Treatment Satisfaction Questionnaire for Medication [TSQM] Scores |
|-----------------|--|

End point description:

TSQM version 1.4 is an instrument to assess subjects' satisfaction with medication. It consists of 13 questions that cover three dimensions (effectiveness, side effects and convenience) plus a global satisfaction question. Four scores ranging from 0 to 100 (extremely satisfied) are obtained. Least-square means were estimated using a MMRM on TSQM score data (treatment group, region of

enrollment, baseline EDSS stratum, visit, treatment-by-visit interaction as factors). ITT population.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 48 weeks             |           |

| End point values                    | Teriflunomide 7 mg  | Teriflunomide 14 mg | Interferon beta-1-a (IFN- $\beta$ -1a) |  |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type                  | Reporting group     | Reporting group     | Reporting group                        |  |
| Number of subjects analysed         | 109                 | 111                 | 104                                    |  |
| Units: Units on a scale             |                     |                     |  |  |
| least squares mean (standard error) |                     |                     |  |  |
| Effectiveness score                 | 67.25 ( $\pm$ 2.7)  | 63.13 ( $\pm$ 2.75) | 59.3 ( $\pm$ 2.97)                     |  |
| Side effects score                  | 95.29 ( $\pm$ 2.31) | 93.15 ( $\pm$ 2.34) | 71.38 ( $\pm$ 2.5)                     |  |
| Convenience score                   | 88.3 ( $\pm$ 1.97)  | 89.85 ( $\pm$ 1.98) | 61.9 ( $\pm$ 2.11)                     |  |
| Global satisfaction score           | 68.29 ( $\pm$ 2.77) | 68.82 ( $\pm$ 2.78) | 60.98 ( $\pm$ 2.94)                    |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Core Treatment Period: Overview of Adverse Events [AEs]

|                 |  |
|-----------------|--|
| End point title | Core Treatment Period: Overview of Adverse Events [AEs] <sup>[6]</sup> |
|-----------------|--|

End point description:

AEs were any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the subject during the study. Safety population: all randomized and treated subjects. Subjects were considered according to the drug actually received. The subject randomized to teriflunomide 14 mg group who received teriflunomide 7 mg was analyzed in the teriflunomide 7 mg group.

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

End point timeframe:

From first study drug intake up to 112 days after last intake in the core treatment period or up to first intake in the extension treatment period, whichever occurred first.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The was data provided for core treatment period only.

| End point values                            | Teriflunomide 14 mg | Interferon beta-1-a (IFN- $\beta$ -1a) | Teriflunomide 7 mg / 14 mg |  |
|---|---------------------|--|----------------------------|--|
| Subject group type                          | Reporting group     | Reporting group                        | Subject analysis set       |  |
| Number of subjects analysed                 | 110                 | 101                                    | 110                        |  |
| Units: subjects                             |                     |  |                            |  |
| Any AE                                      | 102                 | 97                                     | 103                        |  |
| Any serious AE                              | 6                   | 7                                      | 12                         |  |
| Any AE leading to death                     | 0                   | 0                                      | 0                          |  |
| Any AE leading to treatment discontinuation | 12                  | 22                                     | 9                          |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Extension Treatment Period: Overview of AEs

|  |   |
|--|---|
| End point title  | Extension Treatment Period: Overview of AEs |
| End point description:<br>AEs were any unfavourable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the subject during the study. Safety population: subjects were considered in the treatment group to which they were randomized regardless of the drug they actually received. |   |
| End point type   | Secondary                                   |
| End point timeframe:<br>From first intake of study drug in extension treatment period up to 28 days after the last intake in the extension treatment period  |   |

| End point values                               | Teriflunomide<br>14 mg / 14 mg | IFN- $\beta$ -1a /<br>Teriflunomide<br>14 mg | Teriflunomide 7<br>mg / 14 mg |  |
|--|--------------------------------|--|-------------------------------|--|
| Subject group type                             | Reporting group                | Reporting group                              | Subject analysis set          |  |
| Number of subjects analysed                    | 88                             | 59   | 90                            |  |
| Units: subjects                                |                                |  |                               |  |
| Any AE   | 76                             | 48   | 83                            |  |
| Any serious AE                                 | 13                             | 12   | 9                             |  |
| Any AE leading to death                        | 0                              | 0  | 0                             |  |
| Any AE leading to treatment<br>discontinuation | 6                              | 5  | 8                             |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Extension Treatment Period: ARR Poisson Regression Estimates

|   |  |
|---|--|
| End point title   | Extension Treatment Period: ARR Poisson Regression Estimates |
| End point description:<br>ARR was obtained from the total number of confirmed relapses that occurred during the treatment period divided by the sum of the standardized treatment durations. To account for the different treatment durations among subjects, a Poisson Regression Model with robust error variance was used (total number of confirmed relapses as response variable; log-transformed treatment duration as "offset" variable; treatment group, region of enrollment and baseline EDSS stratum as covariates). ITT population. |  |
| End point type  | Secondary  |



---

End point timeframe:

Extension treatment period (Maximum: 197 weeks)

---

| <b>End point values</b>          | Teriflunomide<br>14 mg / 14 mg | IFN- $\beta$ -1a /<br>Teriflunomide<br>14 mg | Teriflunomide 7<br>mg / 14 mg |  |
|----------------------------------|--------------------------------|--|-------------------------------|--|
| Subject group type               | Reporting group                | Reporting group                              | Subject analysis set          |  |
| Number of subjects analysed      | 89                             | 59   | 89                            |  |
| Units: Relapses per year         |                                |  |                               |  |
| number (confidence interval 95%) | 0.193 (0.121<br>to 0.307)      | 0.252 (0.145<br>to 0.438)                    | 0.236 (0.154<br>to 0.362)     |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 197) regardless of seriousness or relationship to Investigational Medicinal Product (IMP).

Adverse event reporting additional description:

The analysis was performed on the safety population as previously defined. Reported adverse events are treatment emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (up to 28 days after the last intake of IMP in the extension study treatment period).

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Core Treatment: Teriflunomide 7 mg |
|-----------------------|------------------------------------|

Reporting group description:

Teriflunomide 7 mg once daily (mean exposure of 456.62 days).

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Core Treatment: Teriflunomide 14 mg |
|-----------------------|-------------------------------------|

Reporting group description:

Teriflunomide 14 mg once daily (mean exposure of 434.43 days).

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Core Treatment: IFN- $\beta$ -1a |
|-----------------------|----------------------------------|

Reporting group description:

Interferon  $\beta$ -1a 3 times a week (mean exposure of 405.18 days).

|                       |  |
|-----------------------|--|
| Reporting group title | Extended Treatment: Teriflunomide 14 mg (After IFN- $\beta$ -1a) |
|-----------------------|--|

Reporting group description:

Teriflunomide 14 mg once daily in extended treatment period after Interferon  $\beta$ -1a 3 times a week in core treatment period (mean exposure of 1000.03 days).

|                       |  |
|-----------------------|--|
| Reporting group title | Extended Treatment: Teriflunomide 14 mg (After 7 mg) |
|-----------------------|--|

Reporting group description:

Teriflunomide 14 mg once daily in extended treatment period after 7 mg in the core treatment period (mean exposure of 996.76 days).

|                       |   |
|-----------------------|---|
| Reporting group title | Extended Treatment: Teriflunomide 14 mg (After 14 mg) |
|-----------------------|---|

Reporting group description:

Teriflunomide 14 mg once daily in extended treatment period after 14 mg in core treatment period (mean exposure of 1015.32 days).

| Serious adverse events  | Core Treatment:<br>Teriflunomide 7 mg | Core<br>Treatment: Terifluno | Core Treatment:<br>IFN- $\beta$ -1a |
|---|---------------------------------------|------------------------------|-------------------------------------|
| Total subjects affected by serious adverse events                   |                                       |                              |                                     |
| subjects affected / exposed   | 12 / 110 (10.91%)                     | 6 / 110 (5.45%)              | 7 / 101 (6.93%)                     |
| number of deaths (all causes)                                       | 0                                     | 0                            | 0                                   |
| number of deaths resulting from adverse events                      |                                       |                              |                                     |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                       |                              |                                     |
| Uterine Leiomyoma   |                                       |                              |                                     |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Uterine Leiomyosarcoma                               |                 |                 |                 |
| subjects affected / exposed                          | 1 / 110 (0.91%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                                   |                 |                 |                 |
| Varicose Vein  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Deep Vein Thrombosis                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematoma  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Venous Stenosis                                      |                 |                 |                 |
| subjects affected / exposed                          | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Pregnancy, puerperium and perinatal conditions       |                 |                 |                 |
| Abortion Spontaneous                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Gait Disturbance                                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Immune system disorders                         |                 |                 |                 |
| Drug Hypersensitivity                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Uterine Haemorrhage                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cervical Polyp                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Nasal Septum Deviation                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Suicide Attempt                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypomania                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Alanine Aminotransferase Increased              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                           | 3 / 110 (2.73%) | 1 / 110 (0.91%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all       | 3 / 3           | 1 / 1           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Injury, poisoning and procedural complications</b> |                 |                 |                 |
| Contusion   |                 |                 |                 |
| subjects affected / exposed                           | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Forearm Fracture                                      |                 |                 |                 |
| subjects affected / exposed                           | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Tibia Fracture  |                 |                 |                 |
| subjects affected / exposed                           | 1 / 110 (0.91%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cardiac disorders</b>                              |                 |                 |                 |
| Coronary Artery Disease                               |                 |                 |                 |
| subjects affected / exposed                           | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Pericarditis  |                 |                 |                 |
| subjects affected / exposed                           | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus Tachycardia                                     |                 |                 |                 |
| subjects affected / exposed                           | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Supraventricular Tachycardia                          |                 |                 |                 |
| subjects affected / exposed                           | 1 / 110 (0.91%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Nervous system disorders                        |                 |                 |                 |
| Carpal Tunnel Syndrome                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic Stroke                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Optic Neuritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sciatica  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Trigeminal Neuralgia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Thrombocytopenia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemolysis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Neutropenia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 110 (0.91%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Vertigo   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 110 (0.91%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Eye Oedema                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Optic Ischaemic Neuropathy                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Duodenal Perforation                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Crohn's Disease                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal Obstruction                          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Erythema Nodosum                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute Kidney Injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Foot Deformity                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral Disc Disorder                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral Disc Protrusion                  |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 110 (0.91%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal Osteoarthritis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Appendicitis Perforated                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bacterial Pyelonephritis                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peritonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tuberculosis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 110 (0.91%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anal Abscess                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Appendicitis                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bacterial Infection                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cervicitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic Sinusitis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 1 / 110 (0.91%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Meningitis Bacterial                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis Acute                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary Tract Infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Metabolism and nutrition disorders</b>       |                 |                 |                 |
| Hyperkalaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 0 / 110 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>  | Extended Treatment:<br>Teriflunomide 14 mg<br>(After IFN-β-1a) | Extended Treatment:<br>Teriflunomide 14 mg<br>(After 7 mg) | Extended Treatment:<br>Teriflunomide 14 mg<br>(After 14 mg) |
|--|--|--|---|
| <b>Total subjects affected by serious adverse events</b>                   |  |  |   |
| subjects affected / exposed  | 12 / 59 (20.34%)   | 9 / 90 (10.00%)  | 13 / 88 (14.77%)  |
| number of deaths (all causes)  | 0  | 0  | 0   |
| number of deaths resulting from adverse events                             |  |  |   |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |  |  |   |
| Uterine Leiomyoma  |  |  |   |
| subjects affected / exposed  | 0 / 59 (0.00%)   | 0 / 90 (0.00%)   | 1 / 88 (1.14%)  |
| occurrences causally related to treatment / all                            | 0 / 0  | 0 / 0  | 0 / 1   |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0  | 0 / 0   |
| Uterine Leiomyosarcoma   |  |  |   |
| subjects affected / exposed  | 0 / 59 (0.00%)   | 0 / 90 (0.00%)   | 0 / 88 (0.00%)  |
| occurrences causally related to treatment / all                            | 0 / 0  | 0 / 0  | 0 / 0   |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0  | 0 / 0   |
| <b>Vascular disorders</b>  |  |  |   |
| Varicose Vein  |  |  |   |
| subjects affected / exposed  | 0 / 59 (0.00%)   | 0 / 90 (0.00%)   | 1 / 88 (1.14%)  |
| occurrences causally related to treatment / all                            | 0 / 0  | 0 / 0  | 0 / 1   |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0  | 0 / 0   |
| Deep Vein Thrombosis   |  |  |   |
| subjects affected / exposed  | 0 / 59 (0.00%)   | 1 / 90 (1.11%)   | 0 / 88 (0.00%)  |
| occurrences causally related to treatment / all                            | 0 / 0  | 0 / 1  | 0 / 0   |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0  | 0 / 0   |
| Haematoma  |  |  |   |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Venous Stenosis                                      |                |                |                |
| subjects affected / exposed                          | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Pregnancy, puerperium and perinatal conditions       |                |                |                |
| Abortion Spontaneous                                 |                |                |                |
| subjects affected / exposed                          | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Gait Disturbance                                     |                |                |                |
| subjects affected / exposed                          | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Immune system disorders                              |                |                |                |
| Drug Hypersensitivity                                |                |                |                |
| subjects affected / exposed                          | 0 / 59 (0.00%) | 1 / 90 (1.11%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Reproductive system and breast disorders             |                |                |                |
| Uterine Haemorrhage                                  |                |                |                |
| subjects affected / exposed                          | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Cervical Polyp                                       |                |                |                |
| subjects affected / exposed                          | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |                |                |                |
| Nasal Septum Deviation                               |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Suicide Attempt                                 |                |                |                |
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypomania                                       |                |                |                |
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| Alanine Aminotransferase Increased              |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 2 / 90 (2.22%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Contusion                                       |                |                |                |
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Forearm Fracture                                |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tibia Fracture                                  |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Coronary Artery Disease                         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pericarditis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sinus Tachycardia                               |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 1 / 90 (1.11%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Supraventricular Tachycardia                    |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Carpal Tunnel Syndrome                          |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemorrhagic Stroke                             |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Optic Neuritis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 1 / 90 (1.11%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sciatica  |                |                |                |
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 59 (0.00%) | 1 / 90 (1.11%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Trigeminal Neuralgia                            |                |                |                |
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Thrombocytopenia                                |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemolysis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neutropenia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ear and labyrinth disorders                     |                |                |                |
| Vertigo   |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| Eye Oedema                                      |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Optic Ischaemic Neuropathy                      |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Gastrointestinal disorders                      |                |                |                |
| Duodenal Perforation                            |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Crohn's Disease                                 |                |                |                |
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intestinal Obstruction                          |                |                |                |
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Cholecystitis                                   |                |                |                |
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Erythema Nodosum                                |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 1 / 90 (1.11%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Acute Kidney Injury                             |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nephrolithiasis                                 |                |                |                |



|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                            | 0 / 59 (0.00%) | 1 / 90 (1.11%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Musculoskeletal and connective tissue disorders</b> |                |                |                |
| Foot Deformity   |                |                |                |
| subjects affected / exposed                            | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Intervertebral Disc Disorder                           |                |                |                |
| subjects affected / exposed                            | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Intervertebral Disc Protrusion                         |                |                |                |
| subjects affected / exposed                            | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Spinal Osteoarthritis                                  |                |                |                |
| subjects affected / exposed                            | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Infections and infestations</b>                     |                |                |                |
| Appendicitis Perforated                                |                |                |                |
| subjects affected / exposed                            | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Bacterial Pyelonephritis                               |                |                |                |
| subjects affected / exposed                            | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Peritonitis  |                |                |                |
| subjects affected / exposed                            | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tuberculosis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 1 / 90 (1.11%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Anal Abscess                                    |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Appendicitis                                    |                |                |                |
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bacterial Infection                             |                |                |                |
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cellulitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 1 / 90 (1.11%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cervicitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Chronic Sinusitis                               |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Meningitis Bacterial                            |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyelonephritis Acute                            |                |                |                |
| subjects affected / exposed                     | 1 / 59 (1.69%) | 0 / 90 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary Tract Infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 1 / 90 (1.11%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urosepsis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 1 / 90 (1.11%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Hyperkalaemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 59 (0.00%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Core Treatment:<br>Teriflunomide 7 mg | Core<br>Treatment:Terifluno | Core Treatment:<br>IFN-β-1a |
|---|---------------------------------------|-----------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events |                                       |                             |                             |
| subjects affected / exposed                           | 85 / 110 (77.27%)                     | 92 / 110 (83.64%)           | 92 / 101 (91.09%)           |
| Vascular disorders                                    |                                       |                             |                             |
| Hypertension  |                                       |                             |                             |
| subjects affected / exposed                           | 0 / 110 (0.00%)                       | 5 / 110 (4.55%)             | 4 / 101 (3.96%)             |
| occurrences (all)                                     | 0                                     | 5                           | 4                           |
| General disorders and administration site conditions  |                                       |                             |                             |
| Fatigue   |                                       |                             |                             |
| subjects affected / exposed                           | 7 / 110 (6.36%)                       | 6 / 110 (5.45%)             | 5 / 101 (4.95%)             |
| occurrences (all)                                     | 7                                     | 6                           | 5                           |

|   |                         |                      |                         |
|---|-------------------------|----------------------|-------------------------|
| Asthenia<br>subjects affected / exposed<br>occurrences (all)  | 3 / 110 (2.73%)<br>3    | 1 / 110 (0.91%)<br>1 | 9 / 101 (8.91%)<br>9    |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 10 / 110 (9.09%)<br>10  | 2 / 110 (1.82%)<br>2 | 3 / 101 (2.97%)<br>3    |
| Influenza Like Illness<br>subjects affected / exposed<br>occurrences (all)                                    | 4 / 110 (3.64%)<br>4    | 4 / 110 (3.64%)<br>4 | 49 / 101 (48.51%)<br>49 |
| Injection Site Erythema<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 110 (0.00%)<br>0    | 0 / 110 (0.00%)<br>0 | 10 / 101 (9.90%)<br>10  |
| Reproductive system and breast disorders<br>Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all) | 3 / 110 (2.73%)<br>3    | 6 / 110 (5.45%)<br>6 | 1 / 101 (0.99%)<br>1    |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)  | 7 / 110 (6.36%)<br>7    | 4 / 110 (3.64%)<br>4 | 1 / 101 (0.99%)<br>1    |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                         | 7 / 110 (6.36%)<br>7    | 1 / 110 (0.91%)<br>1 | 5 / 101 (4.95%)<br>5    |
| Investigations<br>Alanine Aminotransferase Increased<br>subjects affected / exposed<br>occurrences (all)      | 12 / 110 (10.91%)<br>12 | 9 / 110 (8.18%)<br>9 | 30 / 101 (29.70%)<br>30 |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)    | 6 / 110 (5.45%)<br>6    | 2 / 110 (1.82%)<br>2 | 2 / 101 (1.98%)<br>2    |
| Nervous system disorders<br>Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)                 | 6 / 110 (5.45%)<br>6    | 3 / 110 (2.73%)<br>3 | 2 / 101 (1.98%)<br>2    |

|   |                         |                         |                         |
|---|-------------------------|-------------------------|-------------------------|
| Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 4 / 110 (3.64%)<br>4    | 1 / 110 (0.91%)<br>1    | 6 / 101 (5.94%)<br>6    |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 23 / 110 (20.91%)<br>23 | 17 / 110 (15.45%)<br>17 | 26 / 101 (25.74%)<br>26 |
| Sciatica<br>subjects affected / exposed<br>occurrences (all)  | 0 / 110 (0.00%)<br>0    | 0 / 110 (0.00%)<br>0    | 3 / 101 (2.97%)<br>3    |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)  | 14 / 110 (12.73%)<br>14 | 11 / 110 (10.00%)<br>11 | 8 / 101 (7.92%)<br>8    |
| Blood and lymphatic system disorders<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all) | 1 / 110 (0.91%)<br>1    | 2 / 110 (1.82%)<br>2    | 4 / 101 (3.96%)<br>4    |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)              | 1 / 110 (0.91%)<br>1    | 1 / 110 (0.91%)<br>1    | 2 / 101 (1.98%)<br>2    |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)             | 19 / 110 (17.27%)<br>19 | 17 / 110 (15.45%)<br>17 | 9 / 101 (8.91%)<br>9    |
| Abdominal Pain<br>subjects affected / exposed<br>occurrences (all)                                      | 5 / 110 (4.55%)<br>5    | 7 / 110 (6.36%)<br>7    | 2 / 101 (1.98%)<br>2    |
| Abdominal Pain Upper<br>subjects affected / exposed<br>occurrences (all)                                | 7 / 110 (6.36%)<br>7    | 7 / 110 (6.36%)<br>7    | 3 / 101 (2.97%)<br>3    |
| Nausea<br>subjects affected / exposed<br>occurrences (all)  | 10 / 110 (9.09%)<br>10  | 10 / 110 (9.09%)<br>10  | 4 / 101 (3.96%)<br>4    |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)   | 4 / 110 (3.64%)<br>4    | 4 / 110 (3.64%)<br>4    | 0 / 101 (0.00%)<br>0    |
| Vomiting  |                         |                         |                         |

|  |                         |                         |                         |
|--|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)   | 6 / 110 (5.45%)<br>6    | 9 / 110 (8.18%)<br>9    | 4 / 101 (3.96%)<br>4    |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)           | 6 / 110 (5.45%)<br>6    | 22 / 110 (20.00%)<br>22 | 1 / 101 (0.99%)<br>1    |
| Renal and urinary disorders<br>Micturition Urgency<br>subjects affected / exposed<br>occurrences (all)           | 2 / 110 (1.82%)<br>2    | 3 / 110 (2.73%)<br>3    | 1 / 101 (0.99%)<br>1    |
| Musculoskeletal and connective tissue disorders<br>Back Pain<br>subjects affected / exposed<br>occurrences (all) | 10 / 110 (9.09%)<br>10  | 11 / 110 (10.00%)<br>11 | 7 / 101 (6.93%)<br>7    |
| Pain In Extremity<br>subjects affected / exposed<br>occurrences (all)  | 11 / 110 (10.00%)<br>11 | 7 / 110 (6.36%)<br>7    | 4 / 101 (3.96%)<br>4    |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 6 / 110 (5.45%)<br>6    | 7 / 110 (6.36%)<br>7    | 4 / 101 (3.96%)<br>4    |
| Muscle Spasms<br>subjects affected / exposed<br>occurrences (all)  | 6 / 110 (5.45%)<br>6    | 5 / 110 (4.55%)<br>5    | 3 / 101 (2.97%)<br>3    |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 110 (1.82%)<br>2    | 3 / 110 (2.73%)<br>3    | 7 / 101 (6.93%)<br>7    |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)               | 26 / 110 (23.64%)<br>26 | 24 / 110 (21.82%)<br>24 | 17 / 101 (16.83%)<br>17 |
| Urinary Tract Infection<br>subjects affected / exposed<br>occurrences (all)                                      | 8 / 110 (7.27%)<br>8    | 3 / 110 (2.73%)<br>3    | 6 / 101 (5.94%)<br>6    |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)   | 8 / 110 (7.27%)<br>8    | 4 / 110 (3.64%)<br>4    | 2 / 101 (1.98%)<br>2    |

|   |                      |                         |                      |
|---|----------------------|-------------------------|----------------------|
| Upper Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all) | 8 / 110 (7.27%)<br>8 | 11 / 110 (10.00%)<br>11 | 9 / 101 (8.91%)<br>9 |
| Oral Herpes<br>subjects affected / exposed<br>occurrences (all)                       | 9 / 110 (8.18%)<br>9 | 0 / 110 (0.00%)<br>0    | 2 / 101 (1.98%)<br>2 |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                       | 8 / 110 (7.27%)<br>8 | 1 / 110 (0.91%)<br>1    | 3 / 101 (2.97%)<br>3 |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 8 / 110 (7.27%)<br>8 | 9 / 110 (8.18%)<br>9    | 5 / 101 (4.95%)<br>5 |
| Ear Infection<br>subjects affected / exposed<br>occurrences (all)                     | 3 / 110 (2.73%)<br>3 | 2 / 110 (1.82%)<br>2    | 2 / 101 (1.98%)<br>2 |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                   | 5 / 110 (4.55%)<br>5 | 6 / 110 (5.45%)<br>6    | 3 / 101 (2.97%)<br>3 |

| <b>Non-serious adverse events</b>   | Extended Treatment:<br>Teriflunomide 14 mg<br>(After IFN-β-1a) | Extended Treatment:<br>Teriflunomide 14 mg<br>(After 7 mg) | Extended Treatment:<br>Teriflunomide 14 mg<br>(After 14 mg) |
|---|--|--|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                | 48 / 59 (81.36%)   | 72 / 90 (80.00%)   | 65 / 88 (73.86%)  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)                              | 7 / 59 (11.86%)<br>7   | 7 / 90 (7.78%)<br>7  | 9 / 88 (10.23%)<br>9  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 2 / 59 (3.39%)<br>2  | 4 / 90 (4.44%)<br>4  | 4 / 88 (4.55%)<br>4   |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)  | 3 / 59 (5.08%)<br>3  | 0 / 90 (0.00%)<br>0  | 2 / 88 (2.27%)<br>2   |
| Pyrexia   |  |  |   |

|   |                      |                     |                     |
|---|----------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 59 (0.00%)<br>0  | 1 / 90 (1.11%)<br>1 | 1 / 88 (1.14%)<br>1 |
| Influenza Like Illness<br>subjects affected / exposed<br>occurrences (all)                                    | 6 / 59 (10.17%)<br>6 | 2 / 90 (2.22%)<br>2 | 0 / 88 (0.00%)<br>0 |
| Injection Site Erythema<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 59 (0.00%)<br>0  | 0 / 90 (0.00%)<br>0 | 0 / 88 (0.00%)<br>0 |
| Reproductive system and breast disorders<br>Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all) | 0 / 59 (0.00%)<br>0  | 1 / 90 (1.11%)<br>1 | 2 / 88 (2.27%)<br>2 |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)  | 5 / 59 (8.47%)<br>5  | 4 / 90 (4.44%)<br>4 | 2 / 88 (2.27%)<br>2 |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 59 (3.39%)<br>2  | 2 / 90 (2.22%)<br>2 | 1 / 88 (1.14%)<br>1 |
| Investigations<br>Alanine Aminotransferase Increased<br>subjects affected / exposed<br>occurrences (all)      | 2 / 59 (3.39%)<br>2  | 5 / 90 (5.56%)<br>5 | 8 / 88 (9.09%)<br>8 |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)    | 1 / 59 (1.69%)<br>1  | 3 / 90 (3.33%)<br>3 | 0 / 88 (0.00%)<br>0 |
| Nervous system disorders<br>Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 59 (5.08%)<br>3  | 3 / 90 (3.33%)<br>3 | 4 / 88 (4.55%)<br>4 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 0 / 59 (0.00%)<br>0  | 3 / 90 (3.33%)<br>3 | 3 / 88 (3.41%)<br>3 |
| Headache  |                      |                     |                     |



|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)  | 10 / 59 (16.95%)<br>10 | 5 / 90 (5.56%)<br>5    | 3 / 88 (3.41%)<br>3    |
| Sciatica<br>subjects affected / exposed<br>occurrences (all)  | 3 / 59 (5.08%)<br>3    | 1 / 90 (1.11%)<br>1    | 3 / 88 (3.41%)<br>3    |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)  | 3 / 59 (5.08%)<br>3    | 3 / 90 (3.33%)<br>3    | 2 / 88 (2.27%)<br>2    |
| Blood and lymphatic system disorders<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all) | 3 / 59 (5.08%)<br>3    | 1 / 90 (1.11%)<br>1    | 2 / 88 (2.27%)<br>2    |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)              | 5 / 59 (8.47%)<br>5    | 5 / 90 (5.56%)<br>5    | 6 / 88 (6.82%)<br>6    |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)             | 8 / 59 (13.56%)<br>8   | 10 / 90 (11.11%)<br>10 | 15 / 88 (17.05%)<br>15 |
| Abdominal Pain<br>subjects affected / exposed<br>occurrences (all)                                      | 2 / 59 (3.39%)<br>2    | 6 / 90 (6.67%)<br>6    | 3 / 88 (3.41%)<br>3    |
| Abdominal Pain Upper<br>subjects affected / exposed<br>occurrences (all)                                | 4 / 59 (6.78%)<br>4    | 3 / 90 (3.33%)<br>3    | 3 / 88 (3.41%)<br>3    |
| Nausea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 59 (1.69%)<br>1    | 0 / 90 (0.00%)<br>0    | 2 / 88 (2.27%)<br>2    |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)   | 3 / 59 (5.08%)<br>3    | 3 / 90 (3.33%)<br>3    | 1 / 88 (1.14%)<br>1    |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 1 / 59 (1.69%)<br>1    | 2 / 90 (2.22%)<br>2    | 1 / 88 (1.14%)<br>1    |
| Skin and subcutaneous tissue disorders  |                        |                        |                        |

|   |   |   |   |
|---|---|---|---|
| Alopecia<br>subjects affected / exposed<br>occurrences (all)  | 4 / 59 (6.78%)<br>4   | 4 / 90 (4.44%)<br>4   | 1 / 88 (1.14%)<br>1   |
| Renal and urinary disorders<br>Micturition Urgency<br>subjects affected / exposed<br>occurrences (all)  | 3 / 59 (5.08%)<br>3   | 2 / 90 (2.22%)<br>2   | 2 / 88 (2.27%)<br>2   |
| Musculoskeletal and connective tissue disorders<br>Back Pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain In Extremity<br>subjects affected / exposed<br>occurrences (all)<br><br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Muscle Spasms<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia<br>subjects affected / exposed<br>occurrences (all) | 5 / 59 (8.47%)<br>5<br><br>4 / 59 (6.78%)<br>4<br><br>4 / 59 (6.78%)<br>4<br><br>2 / 59 (3.39%)<br>2<br><br>1 / 59 (1.69%)<br>1 | 5 / 90 (5.56%)<br>5<br><br>6 / 90 (6.67%)<br>6<br><br>6 / 90 (6.67%)<br>6<br><br>1 / 90 (1.11%)<br>1<br><br>2 / 90 (2.22%)<br>2 | 6 / 88 (6.82%)<br>6<br><br>4 / 88 (4.55%)<br>4<br><br>3 / 88 (3.41%)<br>3<br><br>2 / 88 (2.27%)<br>2<br><br>1 / 88 (1.14%)<br>1 |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary Tract Infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all)  | 3 / 59 (5.08%)<br>3<br><br>3 / 59 (5.08%)<br>3<br><br>4 / 59 (6.78%)<br>4<br><br>3 / 59 (5.08%)<br>3                            | 11 / 90 (12.22%)<br>11<br><br>8 / 90 (8.89%)<br>8<br><br>4 / 90 (4.44%)<br>4<br><br>2 / 90 (2.22%)<br>2                         | 9 / 88 (10.23%)<br>9<br><br>7 / 88 (7.95%)<br>7<br><br>5 / 88 (5.68%)<br>5<br><br>5 / 88 (5.68%)<br>5                           |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Oral Herpes                 |                |                |                |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 90 (1.11%) | 4 / 88 (4.55%) |
| occurrences (all)           | 0              | 1              | 4              |
| Pharyngitis                 |                |                |                |
| subjects affected / exposed | 5 / 59 (8.47%) | 4 / 90 (4.44%) | 4 / 88 (4.55%) |
| occurrences (all)           | 5              | 4              | 4              |
| Influenza                   |                |                |                |
| subjects affected / exposed | 2 / 59 (3.39%) | 3 / 90 (3.33%) | 2 / 88 (2.27%) |
| occurrences (all)           | 2              | 3              | 2              |
| Ear Infection               |                |                |                |
| subjects affected / exposed | 3 / 59 (5.08%) | 0 / 90 (0.00%) | 1 / 88 (1.14%) |
| occurrences (all)           | 3              | 0              | 1              |
| Gastroenteritis             |                |                |                |
| subjects affected / exposed | 1 / 59 (1.69%) | 7 / 90 (7.78%) | 1 / 88 (1.14%) |
| occurrences (all)           | 1              | 7              | 1              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 25 March 2011   | <p>Following changes were made:</p> <ul style="list-style-type: none"><li>•Extension part of the study was elaborated, which was offered to all subjects randomized in EFC10891/TENERE and completed the treatment period - regardless of study arm (teriflunomide or interferon-beta 1a). This extension was an open-label study with all subjects treated with teriflunomide 14 mg/day. The extension was planned to last 48 weeks.</li><li>•Teriflunomide elimination (washout) period was shortened from 16 weeks to 4 weeks to allow subjects to terminate treatment more rapidly.</li><li>•Concomitant medications were modified, which could interfere with the study based on the updated drug interactions data (CYP2C9 substrate and CYP inducers).</li><li>•Peripheral neuropathy confirmed by electrophysiological tests was added as an alert term.</li><li>•Frequency of sample collection was reduced for PK based on available data of teriflunomide.</li><li>•Clarification regarding reporting of AEs was required from signature of informed consent.</li><li>•Rebif overdose, accountability and compliance, disposition of used syringes/cartridges, and other editorial corrections related to the IMP, were re-defined.</li><li>•Clarification and corrected some inconsistencies throughout the protocol regarding neutropenia.</li></ul> |
| 12 July 2012    | <ul style="list-style-type: none"><li>• Extended the current extension period of the TENERE study up to when teriflunomide was commercially available in the country.</li><li>• Modified the concomitant treatments based on the updated drug interactions data.</li></ul>  |
| 28 January 2013 | <ul style="list-style-type: none"><li>•Reduction of scheduled study visits and visit contents for subjects completed a minimum 18 months/72 weeks in extension phase.</li><li>•Clinical visits were performed every 24 weeks up to the end of treatment, and included adverse event reporting; recording of concomitant medication, vital signs, physical examination; dispense study drugs: accountability/compliance; EDSS /Functional System (FS); clinical laboratory only at EOT visit.</li><li>•Central lab services would not be utilized. Lab tests were performed on local basis for all subjects.</li><li>•Clarification that subjects continued on teriflunomide by obtaining it commercially after ending in this extension study, accelerated elimination procedure and follow-up visits were not required.</li><li>•Updated on the PK handling procedure and sampling time.</li><li>•New information regarding potential drug interactions</li><li>•Dosage reduction of activated charcoal for accelerated elimination procedure (reduced from 50g 4 times daily for 11 days to 50g twice daily for 11 days).</li></ul>   |

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| 09 May 2013 | <ul style="list-style-type: none"> <li>•Reduction of scheduled study visits and visit contents for subjects completed a minimum 72 weeks in extension phase.</li> <li>•Clinical visits was performed every 24 weeks up to the end of treatment, and included adverse event reporting; recording of concomitant medication, vital signs, physical examination; dispense study drugs: accountability/compliance; EDSS / FS; clinical laboratory only at EOT visit.</li> <li>•Central lab services was not be utilized except for post-accelerated elimination PK samples. Lab tests was performed on local basis for all subjects.</li> <li>•Clarification that subjects continued on teriflunomide by obtaining it commercially after ending in this extension study, accelerated elimination procedure and follow-up visits were not required.</li> <li>•Updated the PK handling procedure and sampling time.</li> <li>•New information regarding potential drug interactions.</li> <li>•Dosage reduction of activated charcoal for accelerated elimination procedure (reduced from 50g 4 times daily for 11 days to 50g twice daily for 11 days).</li> </ul> |
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24126064>